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=> s bee venom

L1 7518 BEE VENOM

=> s l1 and polypeptide

L2 502 L1 AND POLYPEPTIDE

=> s l2 and 8 Kd

L3 0 L2 AND 8 KD

=> s l2 and 8

L4 55 L2 AND 8

=> s l4 and Kd

L5 3 L4 AND KD

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L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)

=> d 16 1-2 cbib abs

L6 ANSWER 1 OF 2 MEDLINE
88082757 Document Number: 88082757. PubMed ID: 2446869. Photoaffinity labeling of the K+-channel-associated apamin-binding molecule in smooth muscle, liver and heart membranes. Marqueze B; Seagar M J; Couraud F. (Laboratoire de Biochimie, Centre National de la Recherche Scientifique Unite Associee 1179, Marseille-France.) EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Dec 1) 169 (2) 295-8. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB High-affinity binding sites for mono[125I]iodoapamin were detected in membranes (**Kd** = 59 pM, Bmax = 24 fmol/mg protein) and cultured cells (**Kd** = 69 pM, Bmax = 2.**8** fmol/mg protein) from rat heart and in membranes from guinea-pig ileum (**Kd** = 67 pM, Bmax 42 fmol/mg protein) and liver (**Kd** = 15 pM, Bmax = 43 fmol/mg protein). Binding was stimulated by K+ ions (K0.5 = 0.3-0.5 mM). Covalent labeling with arylazide [125I]iodoapamin derivatives showed that smooth muscle, liver and heart binding molecules are associated with a 85-87-kDa **polypeptide**. A second strongly labeled 57-kDa component was identified in liver membranes only.

L6 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
87133589 Document Number: 87133589. PubMed ID: 3028799.
Receptor-mediated
endocytosis of apamin by liver cells. Strong P N; Evans W H. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Mar 2) 163 (2) 267-73. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The binding and uptake of the **bee venom** toxin apamin, by guinea-pig and rat liver were studied. Guinea-pig liver plasma membranes contain inhibitable, high-affinity binding sites for [125I]monoiodoapamin: **Kd** = 12.6 +/- 0.**8** pM (SE); Bmax = 4.2 +/- 0.2 fmol/mg protein. No binding sites for [125I]monoiodoapamin on rat liver plasma membranes were detected in agreement with the absence of a physiological response to the toxin by rat hepatocytes. [125I]Monoiodoapamin, injected into the portal vein of guinea-pigs, was recovered in an undegraded form in a liver endosome fraction. The uptake of [125I]monoiodoapamin by rat livers was less than 4% of that taken up by guinea-pig livers and there was little evidence of radiolabelled toxin appearing in isolated rat endocytic vesicles. Inhibitable, high-affinity binding sites for [125I]monoiodoapamin were also identified on isolated guinea-pig liver endosomal membranes; **Kd** = 10.6 +/- 3.3 pM; Bmax = 2.5 +/- 0.6 fmol/mg protein. No inhibitable apamin binding sites were detected on rat endosomal membranes. Plasma membranes and endosomal membranes isolated from guinea-pig liver showed a similar spectrum of **polypeptides** to that previously reported for plasma membranes and endosomal membranes isolated from rat liver. The enzymatic composition of guinea-pig endosomes was also similar to that previously reported for rat endosomes. The results indicate that apamin was internalised by receptor-mediated endocytosis by guinea-pig liver cells in an analogous manner to that already shown for a variety of endogenous ligands.

=> s spertini f?/au

L7 414 SPERTINI F?/AU

=> s l7 and bee venom

L8 45 L7 AND BEE VENOM

=> dup remove l8

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L9 19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> d l9 1-19 cbib abs

L9 ANSWER 1 OF 19 MEDLINE DUPLICATE 1
2001226583 Document Number: 21142832. PubMed ID: 11207323.
Antigen-independent suppression of the allergic immune response to **bee venom** phospholipase A(2) by DNA vaccination in CBA/J mice. Jilek S; Barbey C; **Spertini F**; Corthesy B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier Universitaire
Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166

(5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee venom** allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L9 ANSWER 2 OF 19 MEDLINE DUPLICATE 2

2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new **bee venom** allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee venom** (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry. RESULTS: Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence

homology with known proteins. CONCLUSIONS: We have identified and sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L9 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
2001:199768 Document No.: PREV200100199768. Antigen-independent suppression of
the allergic immune response to **bee venom** phospholipase A2 by DNA vaccination in CBA/J mice. Corthesy, Blaise (1); Jilek, Samantha (1); Barbey, Catherine (1); **Spertini, Francois (1)** . (1) Hopital Orthopedique, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (February, 2001) Vol. 107, No. 2, pp. S325. print. Meeting Info.: 57th Annual Meeting of the American Academy of Allergy, Asthma and Immunology New Orleans, Louisiana, USA March 16-21, 2001 ISSN: 0091-6749. Language: English. Summary Language: English.

L9 ANSWER 4 OF 19 MEDLINE DUPLICATE 4
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB To assess the capacity of a peptide-based immunotherapy to induce systemic
tolerance via the nasal route, we designed three long overlapping peptides
of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee venom** allergen. Both prophylactic and
therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic
approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

L9 ANSWER 5 OF 19 MEDLINE DUPLICATE 5
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long peptide immunotherapy down-regulates specific IgE

response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L9 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)

2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G.

CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS

2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenecity trial with phospholipase A2-derived long peptides in **bee venom** hypersensitive patients.

Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary

Language: English.

L9 ANSWER 8 OF 19 MEDLINE DUPLICATE 6
1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and T-cell
responses to high-molecular weight allergens from **bee venom**. Kettner A; Henry H; Hughes G J; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1999 Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Bee venom** contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee venom** desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee venom** allergens >/= 50 kDa. METHODS: **Bee venom** proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee venom** fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee venom** -hypersensitive patients, IgE recognition pattern of **bee venom** allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins >/= 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee venom** elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee venom** allergy may require careful characterization of such allergens.

L9 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint); vonGarnier C; Corradin G P; **Spertini F**. CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; **Spertini, F. (1)**. (1) Dep. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51. Meeting

Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:176527 The Genuine Article (R) Number: YW339. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**.. Astori M (Reprint); Kettner A; Frutiger S; Hughes G J; Corradin G; **Spertini F**. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1998) Vol. 101, No. 1, Part 2, pp. 697-697. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1998:154406 Document No.: PREV199800154406. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori, M.; Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, G.; **Spertini, F.**. Div. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1998) Vol. 101, No. 1 PART 2, pp. S169. Meeting Info.: 54th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Washington, DC, USA March 13-18, 1998 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 13 OF 19 MEDLINE DUPLICATE 7
1998341973 Document Number: 98341973. PubMed ID: 9678833. Delineation of PLA2 epitopes using short or long overlapping synthetic peptides: interest for specific immunotherapy. Kammerer R; Kettner A; Chvatchko Y; Dufour N; Tiercy J M; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1997 Sep) 27 (9) 1016-26. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: Venom immunotherapy is definitely indicated in severe systemic anaphylactic reactions to bee stings, but is not devoided of risks of anaphylaxis. Safer methods of immunotherapy need to be developed. OBJECTIVE: To delineate phospholipase A2 T-cell epitopes using short 15mer vs long 40-60mer overlapping peptides, and to approach the potential interest of a venom immunotherapy based on the use of long peptides (1-60, 51-99, 90-134) mapping the whole phospholipase A2 molecule vs a restricted number of immunodominant epitopes. METHODS: Proliferation of a CD8+ T cell depleted peripheral blood mononuclear cell fraction and short-term T-cell lines from unselected **bee venom** hypersensitive patients in response to phospholipase A2 synthetic peptides. RESULTS: Whereas T-cell proliferation to 15mer overlapping peptides was weak, T-cell response to long overlapping peptides was in contrast vigorous in all patients, mostly directed to C-terminal peptide 90-134. Our results did not support the concept of rare dominant T-cell epitopes, and disclosed T-cell responses to multiple epitopes in several patients. No

significant IgE-binding to long overlapping peptides was detected except in one patient against peptide 90-134. CONCLUSION: 15mer peptides might not be sensitive enough to fully delineate all potential T-cell epitopes scattered along the allergen. Since they do not bind IgE in vitro or only weakly, and taking into account a T-cell response frequently directed to multiple epitopes, long overlapping peptides may represent ideal tools for immunotherapy.

L9 ANSWER 14 OF 19 MEDLINE DUPLICATE 8
97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional **bee venom** immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.
AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2(PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to **bee venom** and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for peptide immunotherapy.

L9 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
96:400023 The Genuine Article (R) Number: UK861. A NOVEL 7.6 KD ALLERGEN FROM **BEE VENOM** - ISOLATION AND CHARACTERIZATION. ASTORI M (Reprint); KETTNER A; FRUTIGER S; HUGHES G J; CORRADIN G; **SPERTINI F.** CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND;

INST BIOCHEM, CH-1066 EPALINGES, SWITZERLAND; CTR MED UNIV GENEVA, DEPT MED BIOL, CH-1211 GENEVA, SWITZERLAND. FASEB JOURNAL (30 APR 1996) Vol. 10, No. 6, pp. 2764. ISSN: 0892-6638. Pub. country: SWITZERLAND.
Language:
ENGLISH.

L9 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer, R.;
Dufour, N.; Corradin, G. (1); **Spertini, F.**. (1) Inst. Biochem., 1066 Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative
Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 17 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310226 Document No.: PREV199699032582. A novel 7.6kD allergen from **bee venom**: Isolation and characterization. Astori, M.
(1); Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, C.; **Spertini, F. (1)**. (1) Div. Immunol. Allergy, Cent. Hosp. Univ. Vaudois, 1011 Lausanne Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative
Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:383183 Document No.: PREV199598397483. T cell response to **bee venom** allergens: Modulation by specific immunotherapy. Kammerer, R. B. (1); Chvatchko, Y. (1); Kettner, A. J.; Corradin, G.; **Spertini, F.**. (1) Div. Immunol. Allergy, CHUV, Lausanne Switzerland. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 436. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

L9 ANSWER 19 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:381846 Document No.: PREV199598396146. T-cell and IgE response to partially purified **bee venom** (BV) allergens. Kettner, A. J. (1); Chvatchko, Y.; Kammerer, R. B.; Corradin, G.; **Spertini, F.**. (1) Inst. Biochem., Lausanne Switzerland. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 208. The 9th International Congress of
Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

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L1          7518 S BEE VENOM
L2           502 S L1 AND POLYPEPTIDE
L3             0 S L2 AND 8 KD
L4            55 S L2 AND 8
L5             3 S L4 AND KD
L6             2 DUP REMOVE L5 (1 DUPLICATE REMOVED)
L7           414 S SPERTINI F?/AU
L8            45 S L7 AND BEE VENOM
L9            19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> s l4 and IgE binding

   4 FILES SEARCHED...
L10            4 L4 AND IGE BINDING

=> dup remove l10

PROCESSING COMPLETED FOR L10
L11            1 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> d l11 cbib abs
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L11 ANSWER 1 OF 1 MEDLINE DUPLICATE 1

92113252 Document Number: 92113252. PubMed ID: 1730869.

Glycosylation-inhibiting factor from human T cell hybridomas constructed from peripheral blood lymphocytes of a **bee venom** -sensitive allergic patient. Thomas P; Gomi H; Takeuchi T; Carini C; Tagaya Y; Ishizaka K. (La Jolla Institute for Allergy and Immunology, CA 92037.) JOURNAL OF IMMUNOLOGY, (1992 Feb 1) 148 (3) 729-37. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Human T cell hybridomas, which constitutively secrete glycosylation inhibiting factor (GIF), were constructed from PBL of an allergic individual who was sensitive to honey **bee venom**. PBMC of the patient were stimulated with either denatured or cyanogen bromide-treated **bee venom** phospholipase A2 (PLA2), and Ag-activated cells were propagated by IL-2 in the presence of human recombinant lipocortin I. T cells obtained in the cultures were fused with a HAT-sensitive mutant of the human lymphoblastoid cell line CEM. Approximately one-third of hybridoma clones constitutively secreted GIF. The GIF-producing hybridomas were CD3+ and bore TCR-alpha beta. GIF formed by unstimulated hybridomas lacked affinity for **bee venom** PLA2. Upon cross-linking of CD3, however, a majority of the GIF-producing hybridomas formed **IgE-binding** factors and GIF, the latter of which had affinity for **bee venom** PLA2. Both nonspecific GIF and Ag-binding GIF from the hybridomas bound to an immunosorbent coupled with the anti-lipomodulin mAb 141-B9. Using an affinity-purified GIF as an immunogen, we established mouse B cell hybridomas that secreted monoclonal anti-human GIF. In order to characterize human nonspecific GIF, one of the GIF-producing hybridomas

was adapted to a serum-free medium, and culture supernatant was fractionated by DEAE-Sepharose column chromatography and by gel filtration. The majority of nonspecific GIF in the culture supernatant was recovered from DEAE-Sepharose by elution of the column with 10 mM Tris-HCl buffer, pH **8**.0, containing 50 mM NaCl. Affinity-purification of GIF in the DEAE Sepharose fraction by using anti-GIF-coupled Affigel, and analysis of the purified GIF by SDS-PAGE revealed that human GIF is a single **polypeptide** chain of 14 to 15 kDa. Gel filtration of both crude and affinity-purified GIF preparations confirmed the molecular size of the cytokine.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	52.79	52.94

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:22:54 ON 16 JUL 2001
Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1644pnh
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 4	Feb 16	TOXLINE no longer being updated
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NEWS 7	May 07	DGENE Reload
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FILE 'HOME' ENTERED AT 15:52:23 ON 16 JUL 2001

=> file medline embase biosis scisearch caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'MEDLINE' ENTERED AT 15:52:41 ON 16 JUL 2001

FILE 'EMBASE' ENTERED AT 15:52:41 ON 16 JUL 2001

FILE 'BIOSIS' ENTERED AT 15:52:41 ON 16 JUL 2001

FILE 'SCISEARCH' ENTERED AT 15:52:41 ON 16 JUL 2001

FILE 'CAPLUS' ENTERED AT 15:52:41 ON 16 JUL 2001
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=> s bee venom

2 FILES SEARCHED...
4 FILES SEARCHED...
L1 7518 BEE VENOM

=> s l1 and polypeptide

1 FILES SEARCHED...
L2 502 L1 AND POLYPEPTIDE

=> s l2 and phospholipase A2

L3 76 L2 AND PHOSPHOLIPASE A2

=> s l3 and hyaluronidase

L4 4 L3 AND HYALURONIDASE

=> dup remove l4

PROCESSING COMPLETED FOR L4
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)

=> d l5 1-2 cbib abs

L5 ANSWER 1 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
1998201277 EMBASE Application of free-flow electrophoresis for isolation and purification of proteins and peptides. Loseva O.I.; Gavryushkin A.V.; Osipov V.V.; Vanyakin E.N.. Dr. A.V. Gavryushkin, State Res. Ctr. Applied Microbiol., Obolensk, Moscow Region 142279, Russian Federation. Electrophoresis 19/7 (1127-1134) 1998.
Refs: 34.
ISSN: 0173-0835. CODEN: ELCTDN. Pub. Country: Germany. Language: English. Summary Language: English.
AB Free-flow electrophoresis (FFE) has been applied to the separation and purification of a variety of proteins and **polypeptides**: **bee venom**, tumor necrosis factor, interleukin-1.beta., interferon-.gamma. and superoxide dismutase. FFE at constant pH and conductivity of the carrying buffer is shown to be efficient at various separation schemes. In some cases, the method allows us to obtain proteins with a purity of more than 90% at a productivity of 20-30 mg/h. An electrophoretic apparatus with a new, multi-sectional construction of the electrophoretic chamber and a system for cross-displacement of carrying buffer in the chamber is described.

L5 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
94339780 EMBASE Document No.: 1994339780. Liquid chromatographic analysis and separation of **polypeptide** components from honey **bee venoms**. Szokan G.; Horvath J.; Almas M.; Saftics G.; Palocz A.. Department of Organic Chemistry, Eotvos University,Eotvos, Budapest, Hungary. Journal of Liquid Chromatography 17/16 (3333-3349) 1994.
ISSN: 0148-3919. CODEN: JLCHD8. Pub. Country: United States. Language: English. Summary Language: English.
AB Reversed-phase HPLC on different columns with acetonitrile-water-trifluoroacetic acid eluent system was used to characterize honey **bee venoms** and to separate and determine quantitatively its peptide components.

=> d his

(FILE 'HOME' ENTERED AT 15:52:23 ON 16 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:52:41 ON 16 JUL 2001
L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)

=> s l2 and allergen C

L6 1 L2 AND ALLERGEN C

=> d 16 cbib abs

L6 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2001 ISI (R)
97:726142 The Genuine Article (R) Number: XX857. Comparison of the antibody response to **bee venom** phospholipase A(2) induced by natural exposure in humans or by immunization in mice. Schneider T (Reprint); Dudler T; Annand R R; Gelb M H; King T P; Suter M. SWISS INST ALLERGY & ASTHMA RES, CH-7270 DAVOS, SWITZERLAND; UNIV WASHINGTON, DEPT CHEM, SEATTLE, WA 98195; UNIV WASHINGTON, DEPT BIOCHEM, SEATTLE, WA 98195;
ROCKEFELLER UNIV, NEW YORK, NY 10021. JOURNAL OF MOLECULAR RECOGNITION (MAR-APR 1997) Vol. 10, No. 2, pp. 93-100. Publisher: JOHN WILEY & SONS LTD. BAFFINS LANE CHICHESTER, W SUSSEX, ENGLAND PO19 1UD. ISSN: 0952-3499.
Pub. country: SWITZERLAND; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Two human and twelve murine monoclonal antibodies directed against the main **bee venom** allergen phospholipase A(2) (PLA) were evaluated for their fine specificity of binding to antigen and their ability to inhibit the enzymatic activity of the antigen, Antibodies were induced by natural exposure of beekeepers to **bee venom** or immunization of mice via different methods, Both human monoclonal antibodies (hmAbs) were previously shown to recognize the native three-dimensional conformation of PLA and are directed against discontinuous epitopes which include lysine residue at position 25 as a contact residue. In contrast, six of the murine monoclonal antibodies (mmAbs) bind to the denatured structure of the protein as determined by enzyme-linked immunosorbent assay, The epitopes recognized are located near the C-terminal end (n=8), in the centre of the **polypeptide** (n=1), near the N-terminal end (n=1) or include the carbohydrate part (n=2) of the PLA molecule, The capacity of the antibodies to modify the enzymatic activity was also determined, The hmAbs significantly inhibit the enzyme (70-79%), whereas the mmAbs produced various degrees of inhibition (39-100%), Since the X-ray structure of PLA is known, the epitopes can be visualized in the context of the three-dimensional structure of the antigen, A qualitative correlation was found between the location of epitopes and the inhibition pattern. Strong inhibition was seen with those antibodies that recognize epitopes that lie on the surface of the enzyme that is thought to contact the phospholipid bilayer, The results show that even though both hmAbs and most mmAbs inhibit the enzymatic activity of PLA, the antigen-binding properties of antibodies from different species raised after different routes of immunization differ significantly, Thus, detailed epitope mapping studies using murine antibodies prepared by artificial immunization may have limited value in predicting epitope patterns relevant to an antibody response to allergens in humans naturally exposed to antigen/**allergen**. (C)

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:52:41 ON 16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)
L6 1 S L2 AND ALLERGEN C

=> s l2 and mellitin

L7 8 L2 AND MELLITIN

=> dup remove l7

PROCESSING COMPLETED FOR L7
L8 8 DUP REMOVE L7 (0 DUPLICATES REMOVED)

=> d l8 1-8 cbib abs

L8 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2001 ACS
1991:401650 Document No. 115:1650 Effect of melittin on renin and prostaglandin E2 release from rat renal cortical slices. Churchill, Paul C.; Rossi, Noreen F.; Churchill, Monique C.; Ellis, Virginia R. (Sch. Med., Wayne State Univ., Detroit, MI, 48201, USA). J. Physiol. (London), 428, 233-41 (English) 1990. CODEN: JPHYA7. ISSN: 0022-3751.
AB Expts. were designed to det. the effect of melittin on renin secretion. Melittin is a **polypeptide** component of **bee venom** which stimulates phospholipase A2 activity, thereby increasing arachidonic acid release and prostaglandin (PG) synthesis, and which inhibits protein kinase C activity. Either of these actions might be expected to stimulate renin secretion, since renin secretion is stimulated by arachidonic acid and by several PGs, and since renin secretion is inhibited by several activators of protein kinase C. In rat renal cortical slices incubated in a buffered and oxygenated physiol. saline soln., 0.1-10 .mu.M melittin produced a concn.-dependent stimulation of both PGE2 synthesis and renin secretion. However, melittin-stimulated renin secretion is independent of melittin-stimulated phospholipase A2 activity, arachidonic acid release, and PG synthesis, since 10 .mu.M quinacrine (a phospholipase A2 antagonist) and 50 .mu.M meclofenamate (a cyclooxygenase antagonist) antagonized basal and melittin-stimulated PGE2 synthesis but had no effects on basal or melittin-stimulated renin secretion. Melittin-stimulated renin secretion was not produced by inhibition of protein kinase C. Ouabain partially antagonized, but did not completely block, melittin-stimulated renin secretion. Thus, melittin-stimulated phospholipase A2 activity probably accounts for stimulated PGE2 prodn., but not for stimulated renin secretion. The mechanism of melittin-stimulated renin secretion is unclear; an effect on protein kinase C does not appear to be involved, and in contrast to the stimulatory effects of a variety of other substances, melittin-stimulated renin secretion is only partially antagonized by ouabain.

L8 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2001 ACS
1987:14911 Document No. 106:14911 Transient dichroism measurements of rotational diffusion and interactions of proteins in erythrocyte

membranes. Cherry, Richard J. (Dep. Chem., Univ. Essex, Colchester/Essex, CO4 3SQ, UK). J. Chem. Soc., Faraday Trans. 2, 82(12), 2105-9 (English) 1986. CODEN: JCFTBS. ISSN: 0300-9238.

AB In human erythrocyte membranes the anion transport protein, band 3, may be selectively labeled with eosin-5-maleimide. This has permitted a detailed study to be made of the rotational dynamics of band 3 by using the flash-induced transient dichroism method. In recent expts. the interaction of the **bee venom polypeptide**, melittin (I), with erythrocyte membranes was investigated. I caused a dramatic loss of rotational mobility of band 3, probably by electrostatic crosslinking of the protein into large relatively immobile aggregates. The concn. of I which produced this effect correlated with the concn. required for cell lysis. This suggests a possible role for I-protein interactions in the biol. activity of the **polypeptide**.

L8 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS

1985:400131 Document No.: BA80:70123. MODE OF INHIBITORY ACTION OF MELITTIN ON SODIUM POTASSIUM ATPASE ACTIVITY OF THE RAT SYNAPTIC MEMBRANE. CHEN C-C; LIN-SHIAU S-Y. PHARMACOLOGICAL INSTITUTE, COLLEGE OF MED., NATIONAL TAIWAN UNIV., TAIPEI, TAIWAN 100.. BIOCHEM PHARMACOL, (1985) 34 (13), 2335-2342. CODEN: BCPCA6. ISSN: 0006-2952. Language: English.

AB The effects of melittin from **bee venom**, cardiotoxin from Formosan cobra verom and ouabain on Na+-K+-ATPase activity of the synaptic membrane isolated from rat cerebral cortex were studied. Melittin was the most potent in inhibiting Na+-K+-ATPase activity. Mg2+-ATPase was less susceptible than Na+-K+-ATPase to the inhibitory action of toxins. High K+ (30 mM) reversed the inhibitory action of **mellitin** on Na+-K+-ATPase but did not affect that of cardiotoxin. A comparison between the effects of ouabain and melittin was studied, using double-reciprocal plots of Na+-K+-ATPase activity against K+. Both were competitive with K+ for binding to the K+ site. A median-effect plot revealed that ouabain and melittin antagonized each other when inhibiting Na+-K+-ATPase. Phosphatidylcholine (PC) was the only one of the phospholipids tested capable of protecting Na+-K+-ATPase from the inhibitory action of melittin but not that of ouabain. The inhibitory action of cardiotoxin on this enzyme was decreased by phosphatidylserine and sphingomyelin, in addition to PC. Evidently, melittin **polypeptide** potently inhibits Na+-K+-ATPase, possibly by binding to the K+ site.

L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS

1980:617130 Document No. 93:217130 Effect of melittin-induced membrane alterations on rat heart adenylate cyclase activity. Lad, Pushkaraj L.; Shier, W. Thomas (Cell Biol. Lab., Salk Inst. Biol. Stud., San Diego, CA, 92138, USA). Arch. Biochem. Biophys., 204(2), 418-24 (English) 1980. CODEN: ABBIA4. ISSN: 0003-9861.

AB Melittin (I), a surface-active, 26-amino-acid **polypeptide** from **bee venom**, has been reported to alter a variety of membrane properties. I induced a biphasic alteration of rat heart microsomal adenylate cyclase (II) activity, stimulating it at low concn.

(<30 .mu.g/mL) and inhibiting it at higher concns. (.gtoreq.100 .mu.g/mL).
I potentiated NaF and 5'-guanylylimidodiphosphate activation of II below 40 .mu.g/mL, but it inhibited at high concns., except in the presence of high concns. of 5'-guanylylimidodiphosphate (10-4M). Basal and F--activated II exhibited no significant change in the Km for ATP in the presence of I <40 .mu.g/mL, but the V was elevated. Potentiation by I of II was obsd. at all concns. of F-, 5'-guanylylimidodiphosphate, and Mg2+ tested. The obsd. effects of I on rat heart II are consistent with its acting by altering the properties of membrane lipids with which the enzyme is assocd.

L8 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
1980:258876 Document No.: BA70:51372. HIGH RESOLUTION PROTON NMR STUDIES OF MONOMERIC MELITTIN IN AQUEOUS SOLUTION. LAUTERWEIN J; BROWN L R; WUETHRICH K. INST. CHIM. ORG., UNIV. LAUS., 2 RUE DE LA BARRE, LAUSANNE, SWITZ.. BIOCHIM BIOPHYS ACTA, (1980) 622 (2), 219-230. CODEN: BBACAQ. ISSN: 0006-3002. Language: English.
AB High resolution 1H-NMR at 360 MHz was used to characterize monomeric melittin [a **polypeptide** of 26 amino acids which composes 50% of the dry weight of **bee venom**] in aqueous solution. The monomeric form of **mellitin** prevailed at 3 mM concentration, pH 3.0 and temperatures between 30 and 90.degree. C, both in the absence of salt and with 6 M guanidium chloride. From comparison with model peptides and studies of the effects of 6 M guanidium chloride and variable temperature on the NMR parameters it was concluded that monomeric **mellitin** is predominantly in an extended flexible form, with the fragments 5-9 and 14-20 more highly structured than the rest of the amino acid sequence. The appearance of a 2nd, low abundant form of monomeric **mellitin**, which is in slow exchange on the NMR time scale with both the more abundant monomeric conformation and aggregated **mellitin**, was attributed to cis-trans isomerism of the peptide bond leu-13-pro-14.

L8 ANSWER 6 OF 8 MEDLINE
78137019 Document Number: 78137019. PubMed ID: 273232. Amino acid sequence of honeybee prepromelittin synthesized in vitro. Suchanek G; Kreil G; Hermodson M A. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1978 Feb) 75 (2) 701-4. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB Translation of melittin messenger RNA from queen **bee** **venom** glands in a cell-free system from wheat germ yielded prepromelittin. Sequence analysis of the labeled in vitro product was performed by automatic Edman degradation of the intact **polypeptide** as well as by analysis of some of its proteolytic fragments. Prepromelittin was shown to be composed of 70 amino acids, two of which have not been identified. The sequence of melittin is located in the COOH-terminal third of the **polypeptide** chain (residues 44--69). Prepromelittin starts with a very hydrophobic pre-region, probably 21 residues long, followed by a pro-part of unusual sequence, containing only alanine, proline, and acidic residues. At least three post-translational reactions are required to convert prepromelittin to **mellitin**.

L8 ANSWER 7 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
74184892 EMBASE Document No.: 1974184892. Hypersensitivity responses to **bee venom** and to **mellitin**. Saelinger C.B.; Higginbotham R.D.. Dept. Microbiol., Hlth Sci. Cent., Louisville, Ky., United States. International Archives of Allergy and Applied Immunology 46/1 (28-37) 1974.
CODEN: IAAAAM. Language: English.

AB **Bee venom** has both antigenic and anaphylactoid properties. Immunization of mice with relatively small amounts of this venom induced both cutaneous and fatal systemic hypersensitivity to appropriate challenge with this material. Equivalent or greater systemic hypersensitivity was also induced by adrenalectomy or by heat stress, and thus a fatal reaction to this venom does not necessarily reflect an allergic condition. All immune and anaphylactoid responses to **bee venom** were reproduced with **mellitin**, a cationic **polypeptide** constituent of this venom. In contrast, enhanced response to phospholipase A was demonstrated only by systemic challenge of venom immunized mice. The results suggest that **mellitin** is an important allergen as well as the major toxic constituent of whole **bee venom**.

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
1965:426213 Document No. 63:26213 Original Reference No. 63:4716f-h A new method for the separation of the components of **bee venom**, especially of the centrally active peptide, apamine. Habermann, E.; Reiz, K. G. (Univ. Wuerzburg, Germany). Biochem. Z., 341(5), 451-66 (German) 1965.

AB From **bee venom** after gel filtration on Sephadex G-50, hyaluronidase, phospholipase A, and the **polypeptide** **mellitin** were obtained. Gel filtration (0.1M HCOONH4, pH 4.5) yields further 2 electrophoretically distinct peptides (FOa and FOp) and a fraction of the new basic peptide apamine, which by chromatography on CM-cellulose (a 1:3 dild. soln.) and lyophilization was further purified (2.3% of the total poison). Apamine produces specific, long lasting excitation of the central nervous system in mice. Phospholipase A was best prepd. (9-fold purification) by pH 6.9 gel filtration and subsequent chromatography on Amberlite in 91% yield. Hyaluronidase was 40-fold purified. Histamine was the only low-mol.-wt. pharmacol. active component.

=> s l2 and adoplain

L9 0 L2 AND ADOPLAIN

=> s l2 and adolapin

L10 14 L2 AND ADOLAPIN

=> dup remove l10

PROCESSING COMPLETED FOR L10
L11 7 DUP REMOVE L10 (7 DUPLICATES REMOVED)

=> d l11 1-7 cbib abs

L11 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS
1987:95798 Document No. 106:95798 **Bee venom adolapin**: effect on thromboxane A2 and prostacyclin plasma levels in rats with model acute inflammation. Shkenderov, S.; Koburova, K.; Chavdarova, V. (State Inst. Control Drugs, Sofia, 1000, Bulg.). Dokl. Bolg. Akad. Nauk, 39(9), 155-7 (English) 1986. CODEN: DBANAD. ISSN: 0366-8681.

AB In rats, **adolapin** (a basic **polypeptide** from **bee venom**) [79029-92-8] (20 .mu.g/kg, s.c.) did not affect the normal blood plasma levels of prostacyclin [35121-78-9] and thromboxane A3 [60114-68-3], but did antagonize the increases in the formation of these compds. in the blood plasma induced by induction of inflammation by injection of carrageenin into the right hind foot pad. **Adolapin** also inhibited cyclooxygenase [39391-18-9] in vitro, but its max. effect was 60-80%. Thus, **adolapin** may have therapeutic effects without causing disturbances of the physiol. balance of the prostaglandin-forming system.

L11 ANSWER 2 OF 7 MEDLINE DUPLICATE 1
86022057 Document Number: 86022057. PubMed ID: 2996298. Further investigation on the antiinflammatory properties of **adolapin**--**bee venom polypeptide**. Koburova K L; Michailova S G; Shkenderov S V. ACTA PHYSIOLOGICA ET PHARMACOLOGICA BULGARICA, (1985) 11 (2) 50-5. Journal code: 1SL; 7512568. ISSN: 0323-9950. Pub. country: Bulgaria. Language: English.

AB **Adolapin** is a basic **polypeptide** (M. W. 11500) isolated from **bee venom**. It showed marked antiinflammatory and analgetic properties and inhibited cyclooxygenase. It was found that **adolapin** inhibited also the activity of **bee venom** phospholipase A2 (7 nmole/ml producing about 80% inhibition of 2.5 nmole/ml phospholipase). In addition it inhibited the lipoxygenase from human platelets (4.5 nmole/ml inhibited about 80% of the activity of 0.8 mg protein/ml). **Adolapin** (20 micrograms/kg) caused an elevation of c-GMP level in rat spleen and brain as well as a decrease of c-AMP in rat spleen. **Adolapin** was tested by the "tail flick" method which allowed the demonstration of its analgetic action. The partial inhibition of the analgetic effect of **adolapin** induced by naloxon, proved the participation of a central mechanism of action. Similar to other nonsteroid analgetics, **adolapin** displayed antipyretic effect (40 micrograms/kg caused an inhibition of the mean temperature rise about 62%.

L11 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
1985:540101 Document No. 103:140101 **Adolapin** effect on histamine release by rat peritoneal mastocytes. Mikhailova, S.; Koburova, K.; Shkenderov, S. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 18, 39-43 (Bulgarian) 1985. CODEN: IDISD4. ISSN: 0323-9438.

AB The effect of **adolapin**, a basic **polypeptide** of **bees venom** with mol. wt. 11,500, on histamine release by peritoneal mastocytes of rats was investigated. Histamine concn. was detd. by a modification of the spectrofluorometric method. At concn. ranging from 0.1 mcg/mL to 200 mcg/mL **adolapin** caused no histamine release whatsoever. At concns. ranging from 1 mcg/mL to 20 mcg/mL, there was up to 60% inhibition of histamine release, provoked by compd. 48/80 (0.3 mcg/mL). The effect of the calcium ionophore A23187 (0.3 mcg/mL) was not influenced by the **polypeptide** concns. tested. The possible relationship between **adolapin**-induced

inhibition of histamine release and its effect on the metab. of arachidonic acid is discussed.

L11 ANSWER 4 OF 7 MEDLINE DUPLICATE 2
85101057 Document Number: 85101057. PubMed ID: 6440766. [Antipyretic effect of a **polypeptide** from **bee venom**--**adolapin**]. Antipiretichen efekt na edin polipeptid ot pchelnata otrova--**adolapin**. Koburova K; Mikhailova S; Shkenderov S. EKSPERIMENTALNA MEDITSINA I MORFOLOGIIA, (1984) 23 (3) 143-8. Journal code: EEB; 0007506. ISSN: 0367-0643. Pub. country: Bulgaria. Language: Bulgarian.

L11 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
1984:1839 Document No. 100:1839 Anaphylactogenic and antigenic properties of **adolapin**, a **polypeptide** isolated from **bee venom**. Koburova, K.; Grigorova, K.; Shkenderov, S.; Gencheva, G. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 16, 95-9 (Bulgarian) 1983. CODEN: IDISD4. ISSN: 0323-9438.

AB Double radial immunodiffusion in agar gel demonstrated that during prolonged immunization of rabbits, **adolapin** [79029-92-8] fails to produce pptg. antibodies. **Adolapin** proves to be a weak anaphylactogen since anaphylactic reactions are obsd. in guinea pigs at doses exceeding as much as 125 times the therapeutic one.

L11 ANSWER 6 OF 7 MEDLINE DUPLICATE 3
82200186 Document Number: 82200186. PubMed ID: 7080045. **Adolapin** --a newly isolated analgetic and anti-inflammatory **polypeptide** from **bee venom**. Shkenderov S; Koburova K. TOXICON, (1982) 20 (1) 317-21. Journal code: VWT; 1307333. ISSN: 0041-0101. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Adolapin** was isolated by a two-step procedure: gel filtration and chromatography on CM cellulose. The molecular mass of the **polypeptide** as determined by SDS electrophoresis and amino acid composition proved to be 11500 and 11092 respectively. **Adolapin** exhibited a potent analgesic effect demonstrated by the "writhing" test (ED50-0,016mg/kg) and by the Randall-Sellito's test (ED50-0,013 mg/kg). The anti-inflammatory activity of **adolapin** was most marked with regard to carrageenin, prostaglandin and adjuvant rat hind paw edemas and adjuvant polyarthritis. The **adolapin** effects are presumably due to its capacity to inhibit the prostaglandin synthase system, following a biphasic dose-response relationship. It is likely that central mechanisms are also involved in the analgetic action of **adolapin**.

L11 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS
1981:561805 Document No. 95:161805 Lipoxygenase inhibiting activity of **adolapin** - an antiinflammatory **polypeptide** from **bee venom**. Koburova, K.; Shkenderov, S. (USSR). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 14, 51-4 (Bulgarian) 1981. CODEN: IDISD4.

AB **Adolapin** [79029-92-8], a peptide from **bee venom** with antiinflammatory activity, inhibits lipoxygenase [9029-60-1]. The max. effect (42% inhibition) is obtained after 15 min preincubation of 2 .times. 10-6M **adolapin** with the enzyme.

=> s l2 and minimine

L12 4 L2 AND MINIMINE

=> dup remove l12

PROCESSING COMPLETED FOR L12
L13 2 DUP REMOVE L12 (2 DUPLICATES REMOVED)

=> d l13 1-2 cbib abs

L13 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
1997:118167 Document No.: PREV199799417370. Chromatographic and membrane purification of **polypeptide** compounds from honey **bee venom**. Klyushnichenko, V. E. (1); Syagailo, Ya. V.. (1) Shemyakin and Ovchinnikov Inst. Bioorganic Chem., Russia Acad. Sci., Ul. Miklukho-Maklaya 16/10, 117871 GSP Moscow V-437 Russia. Journal of Natural Toxins, (1997) Vol. 6, No. 1, pp. 111-119. ISSN: 1058-8108. Language: English.

AB The compounds of venom Apis mellifera contains a set of **polypeptides**: melittin, phospholipase A2, apamin, MCD-peptide, **minimine**, and other substances. The traditional schemes of purification of honey **bee venom** earlier included different types of chromatography. The present work proposes the combination of chromatographic and membrane methods for purification of honey **bee venom**. The main advantage of membrane purification is that melittin in water exists as a monomer (2.7 kD) but at high salt concentration as a tetramer. Phospholipase A2 may exist as a monomer (15.4 kD) and a dimer similar to melittin. The purification scheme covers: alcohol sedimentation, separation of melittin from the rest of phospholipase A2 by means of membranes with exclusion limit of 15 and 5 kD, ion exchange and scale up RP HPLC of melittin. Each step of purification was analyzed by RP HPLC. The purity of the final product under different chromatographic conditions was compared. The melittin was purified from the impurities more than 98% by RP HPLC.

L13 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
72049998 Document Number: 72049998. PubMed ID: 5001226.
Polypeptides minimine and melittin from **bee venom**: effects on Drosophila. Lowy P H; Sarmiento L; Mitchell H K. ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1971 Jul) 145 (1) 338-43. Journal code: 6SK; 0372430. ISSN: 0003-9861. Pub. country: United States. Language: English.

=> s l2 and acid phosphatase

4 FILES SEARCHED...
L14 0 L2 AND ACID PHOSPHATASE

=> s l2 and protease inhibitor

L15 1 L2 AND PROTEASE INHIBITOR

=> d l15 cbib abs

L15 ANSWER 1 OF 1 MEDLINE
84261515 Document Number: 84261515. PubMed ID: 6086337. Molecular properties of the apamin-binding component of the Ca2+-dependent K+ channel. Radiation-inactivation, affinity labelling and solubilization. Schmid-Antomarchi H; Hugues M; Norman R; Ellory C; Borsotto M; Lazdunski M. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1984 Jul 2) 142 (1) 1-6. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany,
Federal Republic of. Language: English.

AB Radiation-inactivation was used to assess the functional size of the apamin-binding component of the Ca2+-dependent K+ channel. The amount of specific binding of 125I-apamin to receptors in synaptic membranes of rat cortex decayed exponentially with increasing doses of ionizing radiation and target size analysis was consistent with a relative molecular mass of 250 000 +/- 20 000 for the 125I-apamin receptor. Analysis on sodium dodecyl sulfate gels following covalent cross-linking of 125I-apamin to its receptor in a synaptosomal membrane preparation from rat cortex revealed a single labelled **polypeptide** chain of Mr = 33 000 +/- 2000 in the presence of **protease inhibitors**. Our results suggest that the Ca2+-dependent K+ channel from rat cortex is an oligomeric structure of Mr = 250 000 +/- 20 000 containing an apamin-binding subunit of Mr = 33 000 +/- 2000. The apamin-binding component of the Ca2+-dependent K+ channel from rat synaptosomes was solubilized using detergents such as sodium cholate or 3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate. Phospholipids did not increase the stability of the apamin-binding component during the solubilization. Binding of apamin to its solubilized receptor is reversible and saturable. The dissociation constant of the apamin-receptor complex is 40-150 pM, the rates constants of association and dissociation being 3.2 X 10(6) M-1s-1 and 1.4 X 10(-4)s-1 respectively. These binding characteristics are similar to those found for the membrane-bound apamin receptor.

=> s l2 and glycosyated IgE binding protein

2 FILES SEARCHED...
L16 0 L2 AND GLYCOSYATED IGE BINDING PROTEIN

=> d his

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:52:41 ON 16 JUL 2001

L1 7518 S BEE VENOM
L2 502 S L1 AND POLYPEPTIDE
L3 76 S L2 AND PHOSPHOLIPASE A2
L4 4 S L3 AND HYALURONIDASE
L5 2 DUP REMOVE L4 (2 DUPLICATES REMOVED)
L6 1 S L2 AND ALLERGEN C
L7 8 S L2 AND MELLITIN
L8 8 DUP REMOVE L7 (0 DUPLICATES REMOVED)
L9 0 S L2 AND ADOPLAIN
L10 14 S L2 AND ADOLAPIN

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L11             7 DUP REMOVE L10 (7 DUPLICATES REMOVED)
L12             4 S L2 AND MINIMINE
L13             2 DUP REMOVE L12 (2 DUPLICATES REMOVED)
L14             0 S L2 AND ACID PHOSPHATASE
L15             1 S L2 AND PROTEASE INHIBITOR
L16             0 S L2 AND GLYCOSYATED IGE BINDING PROTEIN

=> s k3 and analog

L17         552 K3 AND ANALOG

=> s l3 and and analog

MISSING TERM 'AND AND'
The search profile that was entered contains a logical
operator followed immediately by another operator.

=> s l3 and analog

L18           0 L3 AND ANALOG

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  NEWS  3  Feb 06  Engineering Information Encompass files have new names
  NEWS  4  Feb 16  TOXLINE no longer being updated
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NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS  7  May 07  DGENE Reload
NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                 DWPI and DPCI

NEWS EXPRESS  July 11 CURRENT WINDOWS VERSION IS V6.0b,
              CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
              AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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=> s peptide immunotherapy

L1          189 PEPTIDE IMMUNOTHERAPY
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=> s l1 and bee venom

L2 30 L1 AND BEE VENOM

=> dup remove l2

PROCESSING COMPLETED FOR L2
L3 14 DUP REMOVE L2 (16 DUPLICATES REMOVED)

=> d l3 1-14 cbib abs

L3 ANSWER 1 OF 14 MEDLINE DUPLICATE 1
2001262363 Document Number: 21203275. PubMed ID: 11306962. Mechanism of IL-10-induced T cell inactivation in allergic inflammation and normal response to allergens. Akdis C A; Joss A; Akdis M; Blaser K. (Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland.. akdism@siaf.unizh.ch) . INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (2001 Jan-Mar) 124 (1-3) 180-2. Ref: 14. Journal code: BJ7; 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB BACKGROUND: Induction of specific unresponsiveness (tolerance/anergy) in peripheral T cells and recovery by cytokines from the tissue microenvironment represent two key steps in specific immunotherapy (SIT) with whole allergen or antigenic T cell peptides. METHODS: Antigen-specific T cell responses and molecular mechanisms of T cell inactivation were investigated during conventional SIT, T cell epitope **peptide immunotherapy** and natural exposure to **bee venom** in allergic and hyperimmune individuals. RESULTS: T cell unresponsiveness, initiated by autocrine action of IL-10, is characterized by suppressed proliferative and cytokine responses. The unresponsive T cells can be reactivated by different cytokines that may mimic the microenvironmental cytokine influence. IL-10 initiates peripheral tolerance by blocking the CD28 costimulatory signal in T cells. Coprecipitation experiments reveal that upon stimulation CD28 and IL-10 receptor are physically associated in T cells. Accordingly, IL-10 binding to its receptor inhibits CD28 tyrosine phosphorylation, the initial step of the CD28 signaling pathway. This leads to inhibition of phosphatidylinositol 3-kinase p85 binding to CD28. IL-10 only affects T cells that receive a stimulation with low numbers of triggered T cell receptors and that require costimulatory signals by CD28. CONCLUSION: These data demonstrate the pivotal role of autocrine IL-10 and the interaction of its receptor with CD28 in the induction of T cell tolerance as an immunoregulatory mechanism controlling antigen-specific T cell responses. Copyright 2001 S. Karger AG, Basel

L3 ANSWER 2 OF 14 MEDLINE DUPLICATE 2
2000386468 Document Number: 20354865. PubMed ID: 10898500. Allergen-derived long **peptide immunotherapy** down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2),

a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L3 ANSWER 3 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. Spertini F (Reprint); Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L3 ANSWER 4 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:58615 The Genuine Article (R) Number: 273LF. Modulation of Th2 responses by peptide analogues in a murine model of allergic asthma: Amelioration or deterioration of the disease process depends on the Th1 or Th2 skewing characteristics of the therapeutic peptide. Janssen E M; vanOosterhout A J M; vanRensen A J M L; vanEden W; Nijkamp F P; Wauben M H M (Reprint). UNIV UTRECHT, FAC VET MED, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, POB 80165, NL-3508 TD UTRECHT, NETHERLANDS (Reprint); UNIV UTRECHT, FAC VET MED, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, NL-3508 TD UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, NL-3508 TD UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC PHARM, DEPT PHARMACEUT, NL-3508 TD UTRECHT, NETHERLANDS. JOURNAL OF IMMUNOLOGY (15 JAN 2000) Vol. 164, No. 2, pp. 580-588. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0022-1767. Pub. country: NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Allergen-specific CD4(+) Th2 cells play an important role in the immunological processes of allergic asthma, Previously we have shown that, by using the immunodominant epitope OVA(323-339), **peptide immunotherapy** in a murine model of OVA induced allergic asthma, stimulated OVA-specific Th2 cells, and deteriorated airway hyperresponsiveness and eosinophilia. In the present study, we defined

four modulatory peptide analogues of OVA(323-339) with comparable MHC class II binding affinity, These peptide analogues were used for immunotherapy by s.c. injection in OVA-sensitized mice before OVA challenge, Compared with vehicle-treated mice, treatment with the Th2-skewing mild-type peptide and a Th2-skewing partial agonistic peptide (335N-A) dramatically increased airway eosinophilia upon OVA challenge, In contrast, treatment with a Th1-skewing peptide analogue (336E-A) resulted in a significant decrease in airway eosinophilia and OVA-specific IL-4 and IL-5 production, Our data show for the first time that a Th1-skewing peptide analogue of a dominant allergen epitope can modulate allergen-specific Th2 effector cells in an allergic response in vivo, Furthermore, these data suggest that the use of Th1-skewing peptides instead of wild-type peptide may improve **peptide immunotherapy** and may contribute to the development of a successful and safe immunotherapy for allergic patients.

L3 ANSWER 5 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen **peptide immunotherapy**: Results of a safety and immunogenecity trial with phospholipase A2-derived long peptides in **bee venom** hypersensitive patients. Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L3 ANSWER 6 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:308471 The Genuine Article (R) Number: 304VV. Specific **peptide immunotherapy**. Akdis C A (Reprint); Blaser K. SWISS INST ALLERGY & ASTHMA RES, OBERE STR 22, CH-7270 DAVOS, SWITZERLAND (Reprint). REVUE FRANCAISE D ALLERGOLOGIE ET D IMMUNOLOGIE CLINIQUE (APR 2000) Vol. 40, No. 3, pp. 309-317. Publisher: EXPANSION SCI FRANCAISE. 31 BLVD LATOUR MAUBOURG, 75007 PARIS, FRANCE. ISSN: 0335-7457. Pub. country: SWITZERLAND.
Language: English.

L3 ANSWER 7 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:705152 The Genuine Article (R) Number: 353MP. Peptide-mediated immune responses in specific immunotherapy. Haselden B M; Kay A B; Larche M (Reprint). NATL HEART & LUNG INST, IMPERIAL COLL, SCH MED, DOVEHOUSE ST, LONDON SW3 6LY, ENGLAND (Reprint); NATL HEART & LUNG INST, IMPERIAL COLL, SCH MED, LONDON SW3 6LY, ENGLAND. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (AUG 2000) Vol. 122, No. 4, pp. 229-237. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Conventional immunotherapy using whole allergen extracts has been shown to be an effective, disease-modifying treatment in carefully selected

patients with allergic conjunctivo-rhinitis, asthma and bee and wasp venom hypersensitivity. However, this form of therapy is associated with the risk of systemic anaphylaxis, which, when severe, can be life threatening.
A potentially significant reduction in the incidence of IgE-mediated events during immunotherapy may be achieved by the use of short peptides corresponding to T cell epitopes which, by virtue of their size, are incapable of cross-linking allergen-specific IgE bound to the surface of mast cells and basophils, Initial clinical studies have demonstrated degrees of efficacy which have, in some cases, been associated with adverse events occurring immediately or several hours after peptide administration. Preliminary data from studies employing shorter peptides (20 amino acids or less) suggest that improved efficacy may be achieved by using peptides of defined major histocompatibility complex-binding specificity administered in an incremental dose fashion comparable to conventional immunotherapy. This review will discuss the concept of **peptide immunotherapy** and the implications of recent studies, Copyright (C) 2000 S. Karger AG, Basel.

L3 ANSWER 8 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:757120 The Genuine Article (R) Number: 241UT. **Peptide immunotherapy**. Muller U R (Reprint). ZIEGLERSPITAL BERN, MED KLIN, MORILLONSTR 75-91, CH-3001 BERN, SWITZERLAND (Reprint). ALLERGY (OCT 1999) Vol. 54, Supp. [56], pp. 45-46. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538 . Pub. country: SWITZERLAND. Language: English.

L3 ANSWER 9 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:559025 The Genuine Article (R) Number: 215RZ. Opposite effects of immunotherapy with ovalbumin and the immunodominant T-cell epitope on airway eosinophilia and hyperresponsiveness in a murine model of allergic asthma. Janssen E M; Wauben M H M; Jonker E H; Hofman G; VanEden W; Nijkamp F P; vanOosterhout A J M (Reprint). UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, POB 80-082, NL-3508 TB UTRECHT, NETHERLANDS (Reprint); UNIV UTRECHT, FAC PHARM, DEPT PHARMACOL & PATHOPHYSIOL, NL-3508 TB UTRECHT, NETHERLANDS; UNIV UTRECHT, FAC MED VET, DEPT IMMUNOL, INST INFECT DIS & IMMUNOL, NL-3508 TB UTRECHT, NETHERLANDS. AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY (JUL 1999) Vol. 21, No. 1, pp. 21-29. Publisher: AMER LUNG ASSOC. 1740 BROADWAY, NEW YORK, NY 10019. ISSN: 1044-1549. Pub. country: NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB In the present study, we investigated immunotherapy using an entire protein or an immunodominant epitope in a murine model of allergic asthma.
Immunotherapy was performed in ovalbumin (OVA)-sensitized mice before OVA challenge. Mice were treated subcutaneously with OVA, the immunodominant epitope OVA(323-339), Or vehicle. In vehicle-treated animals, repeated OVA challenge induced increased serum levels of OVA-specific immunoglobulin (Ig)G1, IgE, airway eosinophilia, and hyperresponsiveness, compared with saline-challenged animals. In addition, interleukin (IL)-4 and IL-5

production upon OVA restimulation of lung-draining lymph node cells in vitro were significantly increased in OVA-challenged animals. Immunotherapy using OVA significantly reduced airway eosinophilia and hyperresponsiveness. This finding was accompanied by significantly reduced OVA-specific IL-4 and IL-5 production. Further, OVA immunotherapy induced increased serum levels of OVA-specific IgG1, whereas OVA-specific IgG2a and IgE levels were not affected. In contrast to OVA immunotherapy, immunotherapy with OVA323-339 aggravated airway eosinophilia and hyperresponsiveness. OVA-specific IgG1, IgG2a, and IgG serum levels, and in vitro IL-4 and IL-5 production, were not affected. Thus, immunotherapy with protein resulted in beneficial effects on airway eosinophilia and hyperresponsiveness, which coincided with a local reduced T-helper 2 (Th2) response. In contrast, **peptide immunotherapy** aggravated airway hyperresponsiveness and eosinophilia, indicating a local enhanced Th2 response.

L3 ANSWER 10 OF 14 MEDLINE DUPLICATE 3
1998311035 Document Number: 98311035. PubMed ID: 9648701. Successful immunotherapy with T-cell epitope peptides of **bee venom** phospholipase A2 induces specific T-cell anergy in patients allergic to **bee venom**. Muller U; Akdis C A; Fricker M; Akdis M; Blesken T; Bettens F; Blaser K. (Medical Division, Zieglerspital, Bern, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998 Jun) 101 (6 Pt 1) 747-54. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Specific immunotherapy with honeybee venom (BV) is highly effective, but allergic side effects can occur during treatment. Immunotherapy with peptides containing major T-cell epitopes of the relevant allergen or allergens provides an alternative strategy without these problems. OBJECTIVE: The study investigates the immunologic mechanisms and clinical effects of immunotherapy with T-cell epitope peptides of the major BV allergen, the phospholipase A2 (PLA). METHODS: Five patients with IgE-mediated systemic allergic reactions to bee stings were treated with a mixture of three T-cell epitope peptides of PLA. Ten patients allergic to BV receiving whole BV immunotherapy served as control subjects. Increasing doses of the peptide mixture, up to a maintenance dose of 100 microg, were administered subcutaneously within 2 months. The patients were then challenged with PLA and 1 week later with a bee sting. The cellular and humoral immune response was measured in vitro. RESULTS: No allergic side effects were caused by the **peptide immunotherapy**, and all patients tolerated the challenge with PLA without systemic allergic symptoms. Two patients developed mild systemic allergic reactions after the bee sting challenge. After **peptide immunotherapy**, specific proliferative responses to PLA and the peptides in peripheral blood mononuclear cells were decreased in successfully treated patients. The production of TH2 and TH1 cytokines was inhibited, and B cells were not affected in their capacity to produce specific IgE and IgG4 antibodies. Their levels increased after allergen challenge in favor of IgG4. CONCLUSIONS: Immunotherapy of BV allergy with short T-cell peptides of PLA induces epitope-specific anergy in peripheral T cells and changes the specific isotype ratio in a fashion similar to that of conventional immunotherapy in successfully treated patients.

L3 ANSWER 11 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:828329 The Genuine Article (R) Number: 131XK. Immunotherapy with Fel d 1
peptides decreases IL-4 release by peripheral blood T cells of patients allergic to cats. Pene J (Reprint); Desroches A; Paradis L; Lebel B; Farce M; Nicodemus C F; Yssel H; Bousquet J. HOP ARNAUD VILLENEUVE, INSERM U454, 375 AVE DU DOYEN G GIRAUD, F-34295 MONTPELLIER 5, FRANCE (Reprint); HOP ARNAUD VILLENEUVE, CLIN MALAD RESPIRATOIRES, F-34295 MONTPELLIER 5, FRANCE; IMMULOGIC, WALTHAM, MA. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (OCT 1998) Vol. 102, No. 4, Part 1, pp. 571-578. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: FRANCE; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: Cells producing a T-H2-cytokine profile play an important role in the onset and maintenance of atopic diseases, and therefore specific immunotherapy is aimed to induce a switch to cells producing a T-H1- or T-H0-cytokine profile. Recently, a novel form of immunotherapy making use of synthetic peptides from the major cat allergen Fel d 1 has been developed, but its mechanisms of action are unknown.
Objectives: We examined the effects of immunotherapy with Fel dl peptides on the response to bronchial provocation tests (PD20FEV1) with a standardized Fel d 1 cat extract on Fel d 1-specific serum IgE and IgG Levels and in vitro IL-4 and IFN-gamma production.
Methods: Patients allergic to cats received 6 weekly injections of 7.5 mu g (Low dose), 75 mu g (medium dose), or 750 mu g (high dose) of Fel d 1 peptides (25 patients) or a placebo (6 patients). Results: Six weeks after ending immunotherapy, posttreatment PD20FEV1 was not significantly different between the treated and placebo groups. However, in the medium- and high-dose groups there was a significant improvement between baseline and posttreatment days. IL-4 release was significantly reduced in the high dose-treated group ($P < .005$, Wilcoxon W test), whereas it was unchanged in the low or medium dose- and in the placebo-treated groups. In all groups, IFN-gamma, IgE, and IgG levels remained unchanged.
Conclusion: There was no correlation between the improvement of PD20FEV1 and the decrease in IL-4 production, These data suggest that **peptide immunotherapy** may act by shifting, the Fel d 1-induced response of PBMCs in vitro from the T-H2-like to the T-H0-like phenotype.

L3 ANSWER 12 OF 14 MEDLINE DUPLICATE 4
97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional **bee venom** immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.
AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks

of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2(PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to **bee venom** and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for **peptide immunotherapy**.

L3 ANSWER 13 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97220357 EMBASE Document No.: 1997220357. [Immunotherapy with T cell peptides of **bee venom** phospholipase A2]. IMMUNTHERAPIE MIT T-ZELL-PEPTIDEN DER BIENENGIFT-PHOSPHOLIPASE A2. Muller U.R.; Akdis C.A.; Fricker M.; Blaser K.. Prof. Dr. U.R. Muller, Zieglerspital, Medizinische Klinik, CH-3007 Bern, Switzerland. Allergo Journal 6/SUPPL. 1 (S53-S54) 1997.
Refs: 6.
ISSN: 0941-8849. CODEN: ALJOEY. Pub. Country: Germany. Language: German. Summary Language: German; English.
AB 5 patients with a history of bee sting allergy and strongly positive skin tests as well as high titers of **bee venom** and phospholipase A2-specific IgE serum antibodies underwent immunotherapy with an equimolar mixture of three T cell peptides of the major **bee venom** allergen phospholipase A2. A cumulative dose of around 40 .mu.g of the peptide mixture was applied. All patients tolerated a first provocation test with native phospholipase A2 without systemic allergic symptoms, while 2 showed mild symptoms following a sting provocation test. In vitro studies suggest induction of allergen-specific T cell anergy by **peptide immunotherapy**.

L3 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer, R.;

Dufour, N.; Corradin, G. (1); Spertini, F.. (1) Inst. Biochem., 1066 Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

=> d his

(FILE 'HOME' ENTERED AT 12:21:09 ON 23 JUL 2001)

FILE 'MEDLINE, EMBASE, SCISEARCH, BIOSIS, CAPLUS' ENTERED AT 12:21:22 ON 23 JUL 2001

L1 189 S PEPTIDE IMMUNOTHERAPY
L2 30 S L1 AND BEE VENOM
L3 14 DUP REMOVE L2 (16 DUPLICATES REMOVED)

=> s l1 and phospholipase A2

L4 19 L1 AND PHOSPHOLIPASE A2

=> dup remove l4

PROCESSING COMPLETED FOR L4
L5 8 DUP REMOVE L4 (11 DUPLICATES REMOVED)

=> d l5 1-8 cbib abs

L5 ANSWER 1 OF 8 MEDLINE DUPLICATE 1
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long **peptide immunotherapy** down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed **phospholipase A2** (PLA2), a major bee venom allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against

anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L5 ANSWER 2 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen **peptide immunotherapy**: Results of a safety and immunogenicity trial with **phospholipase A2** derived long peptides in bee venom hypersensitive patients. Spertini F (Reprint); Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO
63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L5 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen **peptide immunotherapy**: Results of a safety and immunogenecity trial with **phospholipase A2**-derived long peptides in bee venom hypersensitive patients. Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and
Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L5 ANSWER 4 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:308471 The Genuine Article (R) Number: 304VV. Specific **peptide immunotherapy**. Akdis C A (Reprint); Blaser K. SWISS INST ALLERGY & ASTHMA RES, OBERE STR 22, CH-7270 DAVOS, SWITZERLAND (Reprint). REVUE FRANCAISE D ALLERGOLOGIE ET D IMMUNOLOGIE CLINIQUE (APR 2000) Vol. 40, No.
3, pp. 309-317. Publisher: EXPANSION SCI FRANCAISE. 31 BLVD LATOUR MAUBOURG, 75007 PARIS, FRANCE. ISSN: 0335-7457. Pub. country: SWITZERLAND.
Language: English.

L5 ANSWER 5 OF 8 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:757120 The Genuine Article (R) Number: 241UT. **Peptide immunotherapy**. Muller U R (Reprint). ZIEGLERSPITAL BERN, MED KLIN, MORILLONSTR 75-91, CH-3001 BERN, SWITZERLAND (Reprint). ALLERGY (OCT
1999) Vol. 54, Supp. [56], pp. 45-46. Publisher: MUNKSGAARD INT PUBL LTD.
35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538
. Pub. country: SWITZERLAND. Language: English.

L5 ANSWER 6 OF 8 MEDLINE DUPLICATE 2
1998311035 Document Number: 98311035. PubMed ID: 9648701. Successful immunotherapy with T-cell epitope peptides of bee venom

phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. Muller U; Akdis C A; Fricker M; Akdis M; Blesken T; Bettens F; Blaser K. (Medical Division, Zieglerspital, Bern, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1998 Jun) 101 (6 Pt 1) 747-54. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Specific immunotherapy with honeybee venom (BV) is highly effective, but allergic side effects can occur during treatment. Immunotherapy with peptides containing major T-cell epitopes of the relevant allergen or allergens provides an alternative strategy without these problems. OBJECTIVE: The study investigates the immunologic mechanisms and clinical effects of immunotherapy with T-cell epitope peptides of the major BV allergen, the **phospholipase A2** (PLA). METHODS: Five patients with IgE-mediated systemic allergic reactions to bee stings were treated with a mixture of three T-cell epitope peptides of PLA. Ten patients allergic to BV receiving whole BV immunotherapy served as control subjects. Increasing doses of the peptide mixture, up to a maintenance dose of 100 microg, were administered subcutaneously within 2 months. The patients were then challenged with PLA and 1 week later with a bee sting. The cellular and humoral immune response was measured in vitro. RESULTS: No allergic side effects were caused by the **peptide immunotherapy**, and all patients tolerated the challenge with PLA without systemic allergic symptoms. Two patients developed mild systemic allergic reactions after the bee sting challenge. After **peptide immunotherapy**, specific proliferative responses to PLA and the peptides in peripheral blood mononuclear cells were decreased in successfully treated patients. The production of TH2 and TH1 cytokines was inhibited, and B cells were not affected in their capacity to produce specific IgE and IgG4 antibodies. Their levels increased after allergen challenge in favor of IgG4. CONCLUSIONS: Immunotherapy of BV allergy with short T-cell peptides of PLA induces epitope-specific anergy in peripheral T cells and changes the specific isotype ratio in a fashion similar to that of conventional immunotherapy in successfully treated patients.

L5 ANSWER 7 OF 8 MEDLINE DUPLICATE 3
97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to **phospholipase A2** and **phospholipase A2**-derived peptides by conventional bee venom immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; Spertini F. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on **phospholipase A2**(PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to bee venom and undergoing VIT in response to PLA2 and PLA2 synthetic peptides

were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 weeks of VIT corresponding to the treatment period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for **peptide immunotherapy**
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L5 ANSWER 8 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
97220357 EMBASE Document No.: 1997220357. [Immunotherapy with T cell peptides of bee venom **phospholipase A2**]. IMMUNTHERAPIE MIT T-ZELL-PEPTIDEN DER BIENENGIFT-**PHOSPHOLIPASE A2**.
Muller U.R.; Akdis C.A.; Fricker M.; Blaser K.. Prof. Dr. U.R. Muller, Zieglerspital, Medizinische Klinik, CH-3007 Bern, Switzerland. Allergo Journal 6/SUPPL. 1 (S53-S54) 1997.
Refs: 6.
ISSN: 0941-8849. CODEN: ALJOEY. Pub. Country: Germany. Language: German.
Summary Language: German; English.
AB 5 patients with a history of bee sting allergy and strongly positive skin tests as well as high titers of bee venom and **phospholipase A2**-specific IgE serum antibodies underwent immunotherapy with an equimolar mixture of three T cell peptides of the major bee venom allergen **phospholipase A2**. A cumulative dose of around 40 .mu.g of the peptide mixture was applied. All patients tolerated a first provocation test with native **phospholipase A2** without systemic allergic symptoms, while 2 showed mild symptoms following a sting provocation test. In vitro studies suggest induction of allergen-specific T cell anergy by **peptide immunotherapy**.

=> s l1 and hyaluronidase

L6 0 L1 AND HYALURONIDASE

=> d his

(FILE 'HOME' ENTERED AT 12:21:09 ON 23 JUL 2001)

FILE 'MEDLINE, EMBASE, SCISEARCH, BIOSIS, CAPLUS' ENTERED AT 12:21:22 ON 23 JUL 2001
L1 189 S PEPTIDE IMMUNOTHERAPY

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L2            30 S L1 AND BEE VENOM
L3            14 DUP REMOVE L2 (16 DUPLICATES REMOVED)
L4            19 S L1 AND PHOSPHOLIPASE A2
L5             8 DUP REMOVE L4 (11 DUPLICATES REMOVED)
L6             0 S L1 AND HYALURONIDASE

=> s l1 and hyaluronidase

L7             0 L1 AND HYALURONIDASE

=> s l1 and allergen c

L8             0 L1 AND ALLERGEN C

=> s l1 and mellitin

L9             0 L1 AND MELLITIN

=> s l1 and adolapin

L10            0 L1 AND ADOLAPIN

=> s adolapin

L11           22 ADOLAPIN

=> s l11 and mellitin

L12            0 L11 AND MELLITIN

=> dup remove l11

PROCESSING COMPLETED FOR L11
L13           11 DUP REMOVE L11 (11 DUPLICATES REMOVED)

=> s l13 and bee

L14           11 L13 AND BEE

=> d l14 1-11 cbib abs


L14  ANSWER 1 OF 11      MEDLINE
86022057  Document Number: 86022057.     PubMed ID: 2996298.   Further
      investigation on the antiinflammatory properties of adolapin--
      bee venom polypeptide. Koburova K L; Michailova S G; Shkenderov S
      V. ACTA PHYSIOLOGICA ET PHARMACOLOGICA BULGARICA, (1985) 11 (2) 50-5.
      Journal code: 1SL; 7512568. ISSN: 0323-9950. Pub. country: Bulgaria.
      Language: English.
AB    Adolapin is a basic polypeptide (M. W. 11500) isolated from
      bee venom. It showed marked antiinflammatory and analgetic
      properties and inhibited cyclooxygenase. It was found that
      adolapin inhibited also the activity of bee venom
      phospholipase A2 (7 nmole/ml producing about 80% inhibition of 2.5
      nmole/ml phospholipase). In addition it inhibited the lipoxygenase from
      human platelets (4.5 nmole/ml inhibited about 80% of the activity of 0.8
      mg protein/ml). Adolapin (20 micrograms/kg) caused an elevation
      of c-GMP level in rat spleen and brain as well as a decrease of c-AMP in
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rat spleen. **Adolapin** was tested by the "tail flick" method which allowed the demonstration of its analgetic action. The partial inhibition of the analgetic effect of **adolapin** induced by naloxon, proved the participation of a central mechanism of action. Similar to other nonsteroid analgetics, **adolapin** displayed antipyretic effect (40 micrograms/kg caused an inhibition of the mean temperature rise about 62%.

L14 ANSWER 2 OF 11 MEDLINE
85101057 Document Number: 85101057. PubMed ID: 6440766. [Antipyretic effect of a polypeptide from **bee** venom--**adolapin**]. Antipiretichen efekt na edin polipeptid ot pchelnata otrova--**adolapin**. Koburova K; Mikhailova S; Shkenderov S. EKSPERIMENTALNA MEDITSINA I MORFOLOGIIA, (1984) 23 (3) 143-8. Journal code: EEB; 0007506.
ISSN: 0367-0643. Pub. country: Bulgaria. Language: Bulgarian.

L14 ANSWER 3 OF 11 MEDLINE
82200186 Document Number: 82200186. PubMed ID: 7080045. **Adolapin** --a newly isolated analgetic and anti-inflammatory polypeptide from **bee** venom. Shkenderov S; Koburova K. TOXICON, (1982) 20 (1) 317-21. Journal code: VWT; 1307333. ISSN: 0041-0101. Pub. country: ENGLAND: United Kingdom. Language: English.
AB **Adolapin** was isolated by a two-step procedure: gel filtration and chromatography on CM cellulose. The molecular mass of the polypeptide as determined by SDS electrophoresis and amino acid composition proved to be 11500 and 11092 respectively. **Adolapin** exhibited a potent analgesic effect demonstrated by the "writhing" test (ED50-0,016mg/kg) and by the Randall-Sellito's test (ED50-0,013 mg/kg). The anti-inflammatory activity of **adolapin** was most marked with regard to carrageenin, prostaglandin and adjuvant rat hind paw edemas and adjuvant polyarthritis.
The **adolapin** effects are presumably due to its capacity to inhibit the prostaglandin synthase system, following a biphasic dose-response relationship. It is likely that central mechanisms are also involved in the analgetic action of **adolapin**.

L14 ANSWER 4 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
92154432 EMBASE Document No.: 1992154432. [Wasp and **bee** venom allergies]. WESPE- EN BIJEGIFALLERGIEEN. Kochuyt A.M.. Kliniek voor Inwendige Ziekten, Afdeling Klinische Immunologie, Universitaire Ziekenhuizen,Leuven, Belgium. Tijdschrift voor Geneeskunde 48/8 (565-575)
1992.
ISSN: 0371-683X. CODEN: TGEKBW. Pub. Country: Belgium. Language: Dutch. Summary Language: Dutch.

L14 ANSWER 5 OF 11 SCISEARCH COPYRIGHT 2001 ISI (R)
87:45520 The Genuine Article (R) Number: F6986. **BEE** VENOM **ADOLAPIN** - EFFECT ON THROMBOXANE-A2 AND PROSTACYCLINE PLASMA-LEVELS IN RATS WITH MODEL ACUTE-INFLAMMATION. SHKENDEROV S V (Reprint); KOBOUROVA K A; CHAVDAROVA V. STATE INST CONTROL DRUGS, BU-1000 SOFIA, BULGARIA (Reprint). DOKLADI NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 9, pp. 155-157. Pub. country: BULGARIA. Language: ENGLISH.

L14 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2001 ACS

1985:540101 Document No. 103:140101 **Adolapin** effect on histamine release by rat peritoneal mastocytes. Mikhailova, S.; Koburova, K.; Shkenderov, S. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 18, 39-43 (Bulgarian) 1985. CODEN: IDISD4. ISSN: 0323-9438.

AB The effect of **adolapin**, a basic polypeptide of **bees** venom with mol. wt. 11,500, on histamine release by peritoneal mastocytes of rats was investigated. Histamine concn. was detd. by a modification of the spectrofluorometric method. At concn. ranging from 0.1 mcg/mL to 200 mcg/mL **adolapin** caused no histamine release whatsoever. At concns. ranging from 1 mcg/mL to 20 mcg/mL, there was up to 60% inhibition of histamine release, provoked by compd. 48/80 (0.3 mcg/mL). The effect of the calcium ionophore A23187 (0.3 mcg/mL) was not influenced by the polypeptide concns. tested. The possible relationship between **adolapin**-induced inhibition of histamine release and its effect on the metab. of arachidonic acid is discussed.

L14 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2001 ACS

1984:449848 Document No. 101:49848 Antigenicity of **bee** venom and some of its components. Grigorova, K.; Gencheva, G. (Bulg.). Probl. Infect. Parasit. Dis., 10, 113-16 (English) 1983. CODEN: PIPDD4. ISSN: 0204-9155.

AB The antigenicity of **bee** venom and fraction 1 from **bee** venom was heterogeneous, with .ltoreq.6 and .ltoreq.5 antigen components, resp., being differentiated. Antisera against phospholipase A2 [9001-84-7] and lysophospholipase [9001-85-8] were prepd. and used to demonstrate an antigenic resemblance between the enzymes present in the **bee** venom. Pptg. antibodies against **adolapin** [79029-92-8] could not be prepd. suggesting that **adolapin** was a considerably weaker antigen than the high-mol.-wt. venom components or was an inactive antigen for the exptl. animals used. IgG fractions were isolated from all antisera obtained.

L14 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS

1984:61381 Document No. 100:61381 Anti-inflammatory activity in the venom of Apis mellifera (the common European honey **bee**). Banks, Barbara E. C.; Dempsey, Christopher E.; Barboni, E. (Dep. Physiol., Univ. Coll. London, London, WC1E 6BT, UK). Toxicon, Suppl. 3, 29-32 (English) 1983. CODEN: TOXIA6. ISSN: 0041-0101.

AB Peptide 401 [32908-73-9] and [des Ile]peptide 401 [88640-95-3] but not the transaminated form of peptide 401 caused release of histamine from rat peritoneal mast cells. Therefore, an N-terminal amino group may be essential for the obsd. biol. activity of this **bee** venom constituent peptide. Rats sensitized with Nippostronglus brasiliensis and then challenged with an allergen reduced the swelling caused by carrageenan. Thus, histamine releasing and inflammation inhibiting activities are closely linked. Fractionation of A. mellifera venom was carried out unsuccessfully to identify **adolapin** [79029-92-8] as a high-mol.-wt. peptide with antiinflammatory activity.

L14 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2001 ACS

1984:1839 Document No. 100:1839 Anaphylactogenic and antigenic properties of

adolapin, a polypeptide isolated from **bee** venom.
Koburova, K.; Grigorova, K.; Shkenderov, S.; Gencheva, G. (Bulg.). Izv. -
Durzh. Inst. Kontrol Lek. Sredstva, 16, 95-9 (Bulgarian) 1983. CODEN: IDISD4. ISSN: 0323-9438.
AB Double radial immunodiffusion in agar gel demonstrated that during prolonged immunization of rabbits, **adolapin** [79029-92-8] fails to produce pptg. antibodies. **Adolapin** proves to be a weak anaphylactogen since anaphylactic reactions are obsd. in guinea pigs at doses exceeding as much as 125 times the therapeutic one.

L14 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2001 ACS
1981:561805 Document No. 95:161805 Lipoxygenase inhibiting activity of **adolapin** - an antiinflammatory polypeptide from **bee** venom. Koburova, K.; Shkenderov, S. (USSR). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 14, 51-4 (Bulgarian) 1981. CODEN: IDISD4.
AB **Adolapin** [79029-92-8], a peptide from **bee** venom with antiinflammatory activity, inhibits lipoxygenase [9029-60-1]. The max. effect (42% inhibition) is obtained after 15 min preincubation of 2 .times. 10-6M **adolapin** with the enzyme.

L14 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2001 ACS
1981:97051 Document No. 94:97051 Analgetic effect of **bee** venom and of its **adolapin** peptide components with analgetic and inhibitory effects on prostaglandin synthetase. Shkenderov, S.; Koburova, K. (Bulg.). Izv. - Durzh. Inst. Kontrol Lek. Sredstva, 13, 131-3 (Bulgarian) 1980. CODEN: IDISD4.
AB Analgetic doses (median ED) of crude **bee** venom in the Hendershot mouse test and Randall-Selito rat test were 0.150 and 0.138 mg/kg, resp. Corresponding values for the fraction OA, making up .apprx.25% of lyophilized venom, were 0.022 and 0.020 mg/kg. This fraction had a strong antiinflammatory effect, and at 0.05 mg/kg inhibited by 95% abdominal contractions caused by prostaglandin E. During ion exchange chromatog. of the OA fraction on CM-cellulose, 5 peaks are obtained, the 1st 2 contg. homogeneous peptides named **adolapin** I [76559-67-6] and **adolapin** II [76559-68-7] by the authors. They exert a strong analgetic effect. The latter is explained by the prostaglandin synthetase [9055-65-6] inhibition verified in tests on cat spleen and rat brain.

=> s hyaluronidase

L15 22264 HYALURONIDASE

=> s l15 and bee venom

L16 308 L15 AND BEE VENOM

=> s l16 and therapy

L17 36 L16 AND THERAPY

=> s l17 and vaccine

L18 0 L17 AND VACCINE

=> dup remove l17

PROCESSING COMPLETED FOR L17
L19 27 DUP REMOVE L17 (9 DUPLICATES REMOVED)

=> s l19 and PLA2

L20 1 L19 AND PLA2

=> d l20 cbib abs

L20 ANSWER 1 OF 1 MEDLINE
84008879 Document Number: 84008879. PubMed ID: 6619452. Antibodies to purified **bee venom** proteins and peptides. II. A detailed study of changes in IgE and IgG antibodies to individual **bee venom** antigens. Kemeny D M; MacKenzie-Mills M; Harries M G; Youlten L J; Lessof M H. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1983 Oct) 72 (4) 376-85. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB Antibodies to individual **bee venom** antigens were studied in detail in nine bee sting-allergic patients who received venom immunotherapy without side effects, in two patients who failed to reach maintenance, and in two whose sensitivity returned. The study was confined to patients who had IgE antibodies to at least one of four purified **bee venom** antigens at the start of treatment. IgE and IgG antibodies to phospholipase A2 (**PLA2**), **hyaluronidase** (HYAL), and acid phosphatase (ACID P) and IgE antibodies to melittin (MEL) were measured, and changes in the antibody levels were followed during **bee venom** immunotherapy. Two contrasting patterns of antibody response were seen in the nine successfully treated patients. In five patients there was a rise in serum IgG antibodies to the same antigens as the IgE antibodies. In two patients' serum IgE antibody to HYAL or ACID P fell without a marked IgG antibody response to these antigens, although high levels of IgG antibody to **PLA2** were present in both. Although the first pattern is consistent with a "blocking" role for IgG antibody, clearly the second is not. Not all patients can be conveniently divided into these two categories, and two patients did not show any significant change in either IgG or IgE antibody but were nevertheless able to tolerate the maintenance dose of 100 micrograms of venom. Two patients who failed to reach the maintenance dose of 100 micrograms because of their allergic reactions to the injections of venom were distinguished by (1) very high serum IgE antibody and (2) a low ratio of IgG/IgE antibody. Passive immunization with IgG antibody from a hyperimmune beekeeper was, however, protective in these patients, although it did not raise their overall serum IgG antibody level very much. We are unable to explain either the failure of conventional **therapy** or the beneficial effect of passive immunization in these two patients. Two bee sting--allergic beekeepers lost their sensitivity to stings, but

later, when their sera contained IgE antibody to another **bee venom** antigen, they reacted to stings and inhalation of beehive dander. These data suggest that either falling IgE antibody or IgG-"blocking" antibody could be responsible for providing clinical protection to **bee venom**--allergic subjects. Renewed clinical sensitivity was observed when the IgE response was modulated, with patients making IgE antibody first to one antigen and then to another.

=> s minimine

L21 6 MINIMINE

=> dup remove l21

PROCESSING COMPLETED FOR L21
L22 3 DUP REMOVE L21 (3 DUPLICATES REMOVED)

=> d l22 1-3 cbib abs

L22 ANSWER 1 OF 3 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 1
97:141382 The Genuine Article (R) Number: WG615. Chromatographic and membrane purification of polypeptide compounds from honey bee venom. Klyushnichenk o V E (Reprint); Syagailo Y V. RUSSIAN ACAD SCI, SHEMYAKIN & OVCHINNIKOV INST BIOORGAN CHEM, MOSCOW 117871, RUSSIA. JOURNAL OF NATURAL TOXINS (FEB 1997) Vol. 6, No. 1, pp. 111-119. Publisher: ALAKEN, INC. 305 W MAGNOLIA ST, STE 196, FT COLLINS, CO 80521. ISSN: 1058-8108. Pub. country: RUSSIA.
Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The compounds of venom Apis mellifera contains a set of polypeptides: melittin, phospholipase A2, apamin, MCD-peptide, **minimine**, and other substances. The traditional schemes of purification of honey bee venom earlier included different types of chromatography. The present work proposes the combination of chromatographic and membrane methods for purification of honey bee venom. The main advantage of membrane purification is that melittin in water exists as a monomer (2.7 kD) but at high salt concentration as a tetramer.
Phospholipase A2 may exist as a monomer (15.4 kD) and a dimer similar to melittin. The purification scheme covers: alcohol sedimentation, separation of melittin from the rest of phospholipase A2 by means of membranes with exclusion limit of 15 and 5 kD, ion exchange and scale up RP HPLC of melittin. Each step of purification was analyzed by RP HPLC. The purity of the final product under different chromatographic conditions was compared. The melittin was purified from the impurities more than 98% by RP HPLC.

L22 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
1986:181060 Document No.: BR30:92932. ACUTE RENAL FAILURE DUE TO MULTIPLE STINGS BY AFRICANIZED BEES. MEJIA G; ARBELAEZ M; HENAO J E; SUS A A; ARANGO J L. AP AEREO 60417, MEDELLIN, COLOMBIA, SOUTH AMERICA.. Ann.

Intern. Med., (1986) 104 (2), 210-211. CODEN: AIMEAS. ISSN: 0003-4819. Language: English.

L22 ANSWER 3 OF 3 MEDLINE DUPLICATE 2
72049998 Document Number: 72049998. PubMed ID: 5001226. Polypeptides **minimine** and melittin from bee venom: effects on Drosophila. Lowy P H; Sarmiento L; Mitchell H K. ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1971 Jul) 145 (1) 338-43. Journal code: 6SK; 0372430. ISSN: 0003-9861. Pub. country: United States. Language: English.

=> s acid phosphatase

L23 95436 ACID PHOSPHATASE

=> s l23 and bee venom

L24 91 L23 AND BEE VENOM

=> s l24 and desensitization

L25 2 L24 AND DESENSITIZATION

=> dup remove l25

PROCESSING COMPLETED FOR L25
L26 2 DUP REMOVE L25 (0 DUPLICATES REMOVED)

=> d l26 1-2 cbib abs

L26 ANSWER 1 OF 2 MEDLINE
89277565 Document Number: 89277565. PubMed ID: 2499550. Analysis of differing patterns of cross-reactivity of honeybee and yellow jacket venom-specific IgE: use of purified venom fractions. Wypych J I; Abeyounis C J; Reisman R E. (Department of Medicine, State University of New York, Buffalo.) INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY, (1989) 89 (1) 60-6. Journal code: GP9; 0404561. ISSN: 0020-5915. Pub. country: Switzerland. Language: English.

AB Prior studies of sera from insect sting-allergic patients have analyzed the relationship of coexisting honeybee venom- and yellow jacket venom-specific IgE. Radioallergosorbent (RAST)-inhibition tests with these venoms revealed four different patterns of activity. In this present study, purified fractions prepared from these venoms were used to analyze these varying patterns. The hyaluronidases of yellow jacket venom and honeybee venom showed extensive cross-reaction. The phospholipases from these venoms showed minimal cross-reactivity; antigen 5 was restricted to yellow jacket venom. There was a high molecular weight component in yellow jacket venom with immunologic properties similar to honeybee venom **acid phosphatase**. Sera from individual patients showed quantitative and qualitative differences in the reactions to the major components of both venoms. The differences in the RAST-inhibition patterns in patients with elevated levels of both honeybee venom- and yellow jacket

venom-specific IgE are accounted for by these differences as well as by differences in the cross-reactivity between the individual components.

L26 ANSWER 2 OF 2 MEDLINE
88165469 Document Number: 88165469. PubMed ID: 3349595. IgE and IgG antibody response to purified **bee-venom** antigens and peptides in four patients who had adverse reactions to immunotherapy.
Kemeny D M; Kagey-Sobotka A; Lichtenstein L M; Lessof M H. (Department of Medicine, United Medical, Schools, Guy's Hospital, London, U.K.)
CLINICAL ALLERGY, (1988 Jan) 18 (1) 79-84. Journal code: DBP; 0311172. ISSN: 0009-9090. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The immunological response to individual **bee-venom** allergens was studied in blood samples collected at frequent intervals from four **bee-venom** allergic patients who had suffered systemic allergic reactions to injections of **bee venom** during immunotherapy. All had high IgE antibody levels, at the upper end of the range found in bee-sting allergic patients, and all had antibodies to the minor allergens at the time of the reactions. These did not, however, provide a simple explanation for the reactions that occurred. We were able to observe two interesting phenomena--in one patient IgE antibodies to the individual venom antigens appeared to be 'switched off' sequentially. In another, IgE antibodies to hyaluronidase rose substantially after 4 years of therapy. We believe that these results provide evidence to support the view that the regulation of IgE antibodies is controlled by mechanisms that are both isotype- and antigen-specific.

=> s protease inhibitor

L27 72750 PROTEASE INHIBITOR

=> s l27 and bee venom

L28 33 L27 AND BEE VENOM

=> s l28 and peptide therapy

L29 0 L28 AND PEPTIDE THERAPY

=> s l28 and desensitization

L30 0 L28 AND DESENSITIZATION

=> s l28 and vaccine

L31 0 L28 AND VACCINE

=> s l28 and immune modulation

L32 0 L28 AND IMMUNE MODULATION

=> dup remove l28

PROCESSING COMPLETED FOR L28
L33 19 DUP REMOVE L28 (14 DUPLICATES REMOVED)

=> s l33 and PLAs

L34 0 L33 AND PLAS

=> d l33 1-19 cbib abs

L33 ANSWER 1 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2001:203619 Document No.: PREV200100203619. Use of thiol redox proteins for reducing protein intramolecular disulfide bonds, for improving the quality of cereal products, dough and baked goods and for inactivating snake, bee and scorpion toxins. Buchanan, Bob B. (1); Kobrehel, Karoly; Yee, Boihon C.; Wong, Joshua H.; Lozano, Rosa; Jiao, Jin-an; Shin, Sungho. (1) Berkeley, CA USA. ASSIGNEE: The Regents of the University of California, Cuppertino, CA, USA. Patent Info.: US 6113951 September 05, 2000. Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 5, 2000) Vol. 1238, No. 1, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB Methods of reducing cystine containing animal and plant proteins, and improving dough and baked goods' characteristics is provided which includes the steps of mixing dough ingredients with a thiol redox protein to form a dough and baking the dough to form a baked good. The method of the present invention preferably uses reduced thioredoxin with wheat flour which imparts a stronger dough and higher loaf volumes. Methods for reducing snake, bee and scorpion toxin proteins with a thiol redox (SH) agent and thereby inactivating the protein or detoxifying the protein in an individual are also provided. **Protease inhibitors**, including the Kunitz and Bowman-Birk trypsin inhibitors of soybean, were also reduced by the NADP/thioredoxin system (NADPH, thioredoxin, and NADP-thioredoxin reductase). When reduced by thioredoxin, the Kunitz and Bowman-Birk soybean trypsin inhibitors lose their ability to inhibit trypsin. Moreover, the reduced form of the inhibitors showed increased susceptibility to heat and proteolysis by either subtilisin or a protease preparation from germinating wheat seeds. The 2S albumin of castor seed endosperm was reduced by thioredoxin. Thioredoxin was reduced by either NADPH and NADP-thioredoxin reductase or dithiothreitol. Analyses showed that thioredoxin actively reduced the intramolecular disulfides of the 2S large subunit, but was ineffective in reducing the intermolecular disulfides that connect the large to the small subunit. A novel cystine containing protein that inhibits pullulanase was isolated; thioredoxin reduction of this protein destroyed or greatly reduced its inhibitory activity.

L33 ANSWER 2 OF 19 MEDLINE
2000387536 Document Number: 20269158. PubMed ID: 10811021. Role of various phospholipases A2 and inhibitors in the pathogenesis and prevention of pancreatic acinar cell necrosis: studies with isolated rat pancreatic acini. Mossner J; Wessig C; Ogami Y; Keim V. (Department of Internal Medicine II, University of Leipzig, Germany.. moej@server3.medizin.uni-leipzig.de) . INTERNATIONAL JOURNAL OF PANCREATOLOGY, (2000 Feb) 27 (1) 29-38. Journal code: IJP; 8703511. ISSN: 0169-4197. Pub. country: United States. Language: English.

AB BACKGROUND: Phospholipase A2 (PLA2) may play a central role in the

pathogenesis of pancreatic acinar cell necrosis. Several questions, however, are unsolved: Is acinar cell necrosis caused by PLA2 derived from infiltrating leukocytes or from pancreatic PLA2 itself? Does PLA2 cause cellular lysis by the release of lysolecithin from lecithin or by generation of free radicals? The aims of this study were to determine which form of PLA2 is responsible for cellular damage and how to inhibit its action. METHODS: Isolated rat pancreatic acini were prepared by collagenase digestion. Newly synthesized proteins were labeled by 35S-methionine. Acini were incubated in buffer to which various factors, such as porcine pancreatic PLA2 or **bee venom** PLA2, homogenates of either leukocytes or pancreatic homogenates, all with or without lecithin and with or without potential inhibitors (aprotinin, 4-bromophenacylbromide, BM 16.2115, quinacrine, various analogs of arachidonic acid), or free radicals (hydrogen peroxide, xanthine/xanthine oxidase) with or without allo-purinol or dismutase/catalase were added. Cellular destruction was measured by the release of radiolabeled proteins.
RESULTS: PLA2 alone, free radicals, and granulocytes were not harmful to acini within 30 min of incubation. Free radicals caused significant release of radiolabeled proteins only after 3 h of incubation; this release could be inhibited by scavengers. Incubation of pancreatic acini with PLA2 in combination with lecithin caused rapid release of radiolabeled proteins. Addition of high concentrations of enterokinase activated pancreatic homogenates both alone and with lecithin caused release of cellular proteins, suggesting that pancreatic PLA2 uses lecithin from pancreatic membranes as substrate. Almost all tested potential inhibitors of PLA2 were unable to prevent the destruction caused by either pancreatic or **bee venom** PLA2 and lecithin. However, HK 42, a polyunsaturated fatty acid analog, was able to reduce dose dependently the release of acinar proteins caused by pancreatic PLA2 and lecithin. CONCLUSION: Pancreatic PLA2 and not PLA2 from infiltrating leukocytes may play a role in pancreatic acinar cell necrosis. Cellular lysis is caused upon the action of lysolecithin and probably not via the action of free radicals.

L33 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
2000:368945 Document No.: PREV200000368945. Proteolytic activity of africanized honeybee (Apis mellifera: hymenoptera, apidae) venom. De Lima, P. R. M.; Brochetto-Braga, M. R. (1); Chaud-Netto, J.. (1) Departamento de Biologia, Instituto de Biociencias, 13506-900, Rio Claro, Sao Paulo Brazil. Journal of Venomous Animals and Toxins, (2000) Vol. 6, No. 1 CITED APRIL 18, 2000, pp. 1-14. http://www.scielo.br/cgi-bin/fbpe/fball?got=all&pid=0104-7930&usr=fbpe&lng=en&nrm=iso&sss=1&aut=71981947. online. ISSN: 0104-7930. Language: English. Summary Language: English.
AB Some properties of a Africanized honeybee venom proteases were determined by enzymatic assays in solution, electrophoresis in SDS-PAGE, and gel filtration. **Bee venom** extracts were obtained by reservoir disruption, selective dialysis (cut off 12 kDa) to eliminate small components, such as the **protease inhibitor** present in the venom, and then fractionation of the dialyzed extract by

gel filtration on a Sephadex G-100 column. The optimal conditions for the caseinolytic assays were pH 9.5, 2-hour digestion at 37degree C, and 1% casein concentration. The proteolytic activity was also determined by electrophoresis in SDS-PAGE with co-polymerized gelatin with three major bands of 66.0, 41.6, and 25.1 kDa. A principal serine-protease-like mechanism was revealed in the enriched fraction of proteolytic activity.

L33 ANSWER 4 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
97:6344 The Genuine Article (R) Number: VX807. Toxins affecting K+ channels. Rowan E G (Reprint); Harvey A L. UNIV STRATHCLYDE, DEPT PHYSIOL & PHARMACOL, STRATHCLYDE INST DRUG RES, ROYAL COLL, 204 GEORGE ST, GLASGOW G1 1XW, LANARK, SCOTLAND (Reprint). BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH (DEC 1996) Vol. 29, No. 12, pp. 1765-1780. Publisher: ASSOC BRAS DIVULG CIENTIFICA. FACULDADE MEDICINA, SALA 21, 14049 RIBEIRAO PRETO, SAO PAULO, BRAZIL. ISSN: 0100-879X. Pub. country: SCOTLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Potassium channels are involved in modulating the excitability of neurones by regulating the membrane potential, or by affecting the amount of neurotransmitter released from nerve terminals. Potassium channels are highly diverse and can be activated by either voltage or increased intracellular calcium concentration. The potassium channel forms a highly selective membrane pore. Four subunits each with six membrane-spanning regions (S1-S6) are required to produce a functional pore. Molecular biologists have cloned more than 50 different potassium channel subtypes. Naturally occurring protein toxins have been used to pharmacologically characterize native and cloned potassium channels.

L33 ANSWER 5 OF 19 MEDLINE
97035391 Document Number: 97035391. PubMed ID: 8875913. Inhibition of spiralin processing by the lipopeptide antibiotic globomycin. Beven L; Le Henaff M; Fontenelle C; Wroblewski H. (Equipe "Membranes et Osmoregulation," CNRS URA No. 256, Universite de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France.) CURRENT MICROBIOLOGY, (1996 Nov) 33 (5) 317-22. Journal code: BMW; 7808448. ISSN: 0343-8651. Pub. country:
United States. Language: English.
AB The cyclic lipopeptide globomycin, a specific inhibitor of signal-peptidase II (Lsp A), proved toxic for the mollicute Spiroplasma melliferum with a minimal inhibitory concentration (MIC) in the range 6.25-12.5 microM, about one order of magnitude higher (that is, less efficient) than **bee-venom** mellitin. SDS-PAGE analysis of cell proteins followed by immunolabeling ("Western blotting") and by crossed immunoelectrophoresis demonstrated that the cleavage of the prespiralin leader peptide was prevented by globomycin. Cell fractionation experiments showed that prespiralin was membrane bound and did not accumulate in the cytoplasm or in the culture medium. Furthermore, the use of the potential-sensitive fluorescent dye 3,3'-dipropyl-2,2'-thiadicarbocyanine iodide (diS-C3-[5]) revealed that, in contrast to valinomycin and mellitin, globomycin up to 30 microM has no effect on the electrical transmembrane potential of S. melliferum. This indicates that the toxicity of globomycin for spiroplasma cells is mainly if not exclusively owing to the inhibition of spiralin processing. Added to previously published data, these results suggest that spiralin and probably other lipoproteins of mollicutes are acylated and membrane targeted by a mechanism involving notably the processing of the

prelipoprotein precursor by a type II, globomycin-sensitive signal peptidase.

L33 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2001 ACS
1993:471275 Document No. 119:71275 Use of thio redox proteins for reducing disulfide bonds to improve feed and cereal products and to inactivate snake toxins and insect and scorpion venoms. Buchanan, Bob B.; Kobrehel, Karoly; Yee, Boihon C.; Wong, Joshua H.; Lozano, Rosa; Jiao, Jinan (University of California, USA). PCT Int. Appl. WO 9308274 A1 19930429, 199 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US8595 19921008.
PRIORITY: US 1991-776109 19911012; US 1992-935002 19920825.
AB Thiol redox proteins are used to reduce seed proteins such as cereal proteins, enzyme inhibitor proteins, venom toxin proteins, and the intramol. disulfide bonds of certain other proteins. Thioredoxin and glutaredoxin can be used to reduce gliadins, glutenins, albumins, and globulins to improve the characteristics of dough and baked goods and create new doughs, and to reduce cystine-contg. proteins such as amylase and trypsin inhibitors so as to improve the quality of feed and cereal products. A novel pullulanase inhibitor is isolated. Its activity may be inhibited by the thiol redox proteins. The 2S albumins of oil-bearing seeds (e.g., Ricinus communis) can be reduced with thioredoxin. Reduced thiol redox agents can inactivate snake neurotoxins and certain insect and scorpion venom toxins in vitro and to treat the corresponding toxicities in individuals.

L33 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1993:507500 Document No.: PREV199396131507. Role of sodium potassium pump in herpes simplex type 1-induced cell fusion: Melittin causes specific reversion of syncytial mutants with the Syn1 mutation to Syn-plus (wild-type) phenotype. Baghian, Abolghasem; Kousoulas, Konstantin G. (1). (1) Dep. Veterinary Microbiology Parasitology, Sch. Veterinary Med., Louisiana State Univ., Baton Rouge, LA 70803 USA. Virology, (1993) Vol. 196, No. 2, pp. 548-556. ISSN: 0042-6822. Language: English.
AB To evaluate the importance of the Na+,K+ pump and ionic gradients in virus-induced cell fusion, we investigated the effects of melittin, a 26 amino acid bioactive peptide found in honey **bee venom**, on cell fusion caused by HSV-1 syncytial mutants. Melittin inhibited fusion of Vero cells caused by HSV-1 mutant viruses mP(MP), KOS (syn20) and KOS (FFV3) containing the syncytial mutation syn1 in glycoprotein K. However, it did not affect cell fusion caused by mutants HFEM(tsB5) or KOS amb1511-7 with mutations in glycoprotein B. Melittin caused specific reversion of syn1 mutant virus plaques to syn+ (wild-type) plaque morphology, and inhibited virus adsorption and penetration. It also inhibited the Na+,K+ pump activity, and the binding of 3H-ouabain to the Na+,K+ pump of infected Vero cells. The Na+,K+ pump activity of infected Vero cells in comparison to mock-infected cells was significantly decreased. Ouabain, a specific inhibitor of the Na+,K+ pump, inhibited fusion of Vero cells caused by all syncytial virus strains.

L33 ANSWER 8 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
93:1395 The Genuine Article (R) Number: KC026. NEUROPHARMACOLOGY OF

POTASSIUM-ION CHANNELS. HARVEY A L (Reprint). UNIV STRATHCLYDE, DEPT PHYSIOL & PHARMACOL, GLASGOW G1 1XW, SCOTLAND (Reprint); UNIV STRATHCLYDE, STRATHCLYDE INST DRUG RES, GLASGOW G1 1XW, SCOTLAND. MEDICINAL RESEARCH REVIEWS (JAN 1993) Vol. 13, No. 1, pp. 81-104. ISSN: 0198-6325. Pub. country: SCOTLAND. Language: ENGLISH.

L33 ANSWER 9 OF 19 MEDLINE DUPLICATE 2
88209451 Document Number: 88209451. PubMed ID: 3130091. Inhibition of beta-bungarotoxin binding to brain membranes by mast cell degranulating peptide, toxin I, and ethylene glycol bis (beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid. Schmidt R R; Betz H; Rehm H. (Zentrum fur Molekulare Biologie, Universitat Heidelberg, Federal Republic of Germany.) BIOCHEMISTRY, (1988 Feb 9) 27 (3) 963-7. Journal code: A0G; 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.
AB The presynaptically active snake venom neurotoxin beta-bungarotoxin (beta-Butx) is known to affect neurotransmitter release by binding to a subtype of voltage-activated K+ channels. Here we show that mast cell degranulating (MCD) peptide from **bee venom** inhibits the binding of 125I-labeled beta-Butx to chick and rat brain membranes with apparent Ki values of 180 nM and 1100 nM, respectively. The mechanism of inhibition by MCD peptide is noncompetitive, as is inhibition of 125I-beta-Butx binding by the **protease inhibitor** homologue from mamba venom, toxin I. Beta-Butx and its binding antagonists thus bind to different sites of the same membrane protein. Removal of Ca2+ by ethylene glycol bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid inhibits the binding of 125I-beta-Butx by lowering its affinity to brain membranes.

L33 ANSWER 10 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 3
87:45519 The Genuine Article (R) Number: F6986. ANTIINFLAMMATORY EFFECT OF **BEE VENOM PROTEASE INHIBITOR** ON A MODEL SYSTEM OF ACUTE-INFLAMMATION EDEMA. SHKENDEROV S V (Reprint). STATE INST CONTROL DRUGS, 26 BLVD VL ZAIMOV, SOFIA, BULGARIA (Reprint). DOKLADI NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 9, pp. 151-154. Pub. country: BULGARIA. Language: ENGLISH.

L33 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2001 ACS
1987:65598 Document No. 106:65598 Inhibition of complement activity by certain **bee venom** components. Gencheva, G.; Shkenderov, S. (State Inst. Drug Control, Sofia, Bulg.). Dokl. Bolg. Akad. Nauk, 39(9), 137-9 (English) 1986. CODEN: DBANAD. ISSN: 0366-8681.
AB Protein components of **bee venom** decreased the hemolytic activity of complement. Apamin, but not melittin or the **protease inhibitor** in **bee venom**, was primarily responsible for the activity.

L33 ANSWER 12 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R) DUPLICATE 4
87:37536 The Genuine Article (R) Number: F5416. **BEE VENOM PROTEASE INHIBITOR** - IMPROVED PURIFICATION METHOD AND IDENTIFICATION OF 2 MOLECULAR-FORMS. SHKENDEROV S (Reprint); HABERMANN E; SAMEJIMA Y. JUSTUS LIEBIG UNIV, INST PHARMACOL, FRANKFURTER STR 107,

GIESSEN 1, FED REP GER (Reprint); STATE INST CONTROL DRUGS, SOFIA, BULGARIA. DOKLADI NA BOLGARSKATA AKADEMIYA NA NAUKITE (1986) Vol. 39, No. 8, pp. 69-71. Pub. country: GERMANY; BULGARIA. Language: ENGLISH.

L33 ANSWER 13 OF 19 MEDLINE

84261515 Document Number: 84261515. PubMed ID: 6086337. Molecular properties of the apamin-binding component of the Ca2+-dependent K+ channel. Radiation-inactivation, affinity labelling and solubilization. Schmid-Antomarchi H; Hugues M; Norman R; Ellory C; Borsotto M; Lazdunski M. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1984 Jul 2) 142 (1) 1-6. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany,
Federal Republic of. Language: English.

AB Radiation-inactivation was used to assess the functional size of the apamin-binding component of the Ca2+-dependent K+ channel. The amount of specific binding of 125I-apamin to receptors in synaptic membranes of rat cortex decayed exponentially with increasing doses of ionizing radiation and target size analysis was consistent with a relative molecular mass of 250 000 +/- 20 000 for the 125I-apamin receptor. Analysis on sodium dodecyl sulfate gels following covalent cross-linking of 125I-apamin to its receptor in a synaptosomal membrane preparation from rat cortex revealed a single labelled polypeptide chain of Mr = 33 000 +/- 2000 in the presence of **protease inhibitors**. Our results suggest that the Ca2+-dependent K+ channel from rat cortex is an oligomeric structure of Mr = 250 000 +/- 20 000 containing an apamin-binding subunit of Mr = 33 000 +/- 2000. The apamin-binding component of the Ca2+-dependent K+ channel from rat synaptosomes was solubilized using detergents such as sodium cholate or 3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate. Phospholipids did not increase the stability of the apamin-binding component during the solubilization. Binding of apamin to its solubilized receptor is reversible and saturable. The dissociation constant of the apamin-receptor complex is 40-150 pM, the rates constants of association and dissociation being 3.2 X 10(6) M-1s-1 and 1.4 X 10(-4)s-1 respectively. These binding characteristics are similar to those found for the membrane-bound apamin receptor.

L33 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:529131 Document No. 87:129131 Homology of functionally diverse proteins. Strydom, Daniel J. (Natl. Chem. Res. Lab., CSIR, Pretoria, S. Afr.). J. Mol. Evol., 9(4), 349-61 (English) 1977. CODEN: JMEVAU.

AB Disulfide-rich proteins of widely differing functions were aligned, using their half-cystinyl residues. This led to the grouping of RNase, phospholipase A, lysozyme, snake venom toxins, bee and scorpion venom peptides, and the plant proteins, potato carboxypeptidase inhibitor, ragweed pollen allergen, mistletoe toxins, and pineapple sulfhydryl **protease inhibitor**, into 1 superfamily of proteins. Very few deletions/insertions were needed to effect alignment; probabilities were calcd. for random occurrence of the matches that were found.

L33 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:183279 Document No. 86:183279 New pharmacobiochemical data on the anti-inflammatory effect of **bee venom**. Shkenderov, S. (Biochem. Dep., Inst. State Control Drugs, Sofia, Bulg.). Anim., Plant Microb. Toxins, Proc. Int. Symp., 4th, Meeting Date 1974, Volume 2, 319-36. Editor(s): Ohsaka, Akira; Hayashi, Kyozo; Sawai, Yoshio.

New York, N. Y. (English) 1976. CODEN: 35FUAR.

AB Chromatog. fractions (Oa, Op, and the **protease inhibitor** [37205-61-1]) and pure proteins and peptides from **bee venom** (melittin [37231-28-0], apamin [24345-16-2], and phospholipase A [9001-84-7]) were tested in accordance with some of the tests for nonsteroid anti-inflammatory drugs. Adjuvant arthritis, with doses of 100 .mu.g/kg, was weakly affected by melittin and apamin and moderately affected by the **protease inhibitor** and the fractions Oa and Op. Phospholipase A aggravated the development of adjuvant inflammation. The inflammatory rise of the levels of haptoglobin and .beta.-glucuronidase with adjuvant arthritis was considerably inhibited under the effect of the **bee venom** components examd., with the exception of phospholipase, which does not manifest any inhibitory effect. Seromucoid and haptoglobin also decreased in the case of granuloma pouch and turpentine inflammation under the effect of apamin. In the hind paw edema tests, the inhibition of the carrageenin and prostaglandin E1 inflammation under the effects of Oa and Op fractions and the **protease inhibitor** show immunosuppressive actions. The test for protection of denaturation of the serum proteins was pos. with melittin and apamin. The Oa fraction strongly inhibited gelatin-induced aggregation of erythrocytes. Melittin and the **protease inhibitor** inhibited macrophage migration.

L33 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS

1977:167002 Document No. 86:167002 Further purification, inhibitory spectrum, and some kinetic properties of the **protease inhibitor** in **bee venom**. Shkenderov, S. (Inst. State Control Drugs, Sofia, Bulg.). Anim., Plant Microb. Toxins, Proc. Int. Symp., 4th, Meeting Date 1974, Volume 1, 263-72. Editor(s): Ohsaka, Akira; Hayashi, Kyozo; Sawai, Yoshio. Plenum: New York, N. Y. (English) 1976. CODEN: 35FUAR.

AB A polyvalent proteinase inhibitor was purified from **bee venom** by gel filtration on Sephadex G-50, chromatog. on SP-Sephadex C-25, affinity chromatog. on trypsin-Sepharose, and gel filtration on Sephadex G-15, which resulted not only in desalting but in further sepn. The purified inhibitor was homogeneous as judged by polyacrylamide gel electrophoresis and N-terminal amino acid anal. The N-terminal amino acid was L-lysine. The inhibitory spectrum of the **bee venom** inhibitor strongly resembled Trasylol except that it did not inhibit kallikrein or urokinase. Trypsin and chymotrypsin were most strongly inhibited. Inhibition of trypsin hydrolysis of casein was noncompetitive, whereas inhibition of trypsin amidase activity toward N-benzoyl-DL-arginine-p-nitroanilide was competitive. Inhibition of esterase activities of trypsin and chymotrypsin (toward N-benzoyl-DL-arginine Et ester and N-acetyl-L-tyrosine Et ester, resp.) was competitive. The highest inhibitory activity was obsd. at the onset of the reaction and the inhibitor was thus classified as fast-acting.

L33 ANSWER 17 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5

76024135 EMBASE Document No.: 1976024135. Further purification, inhibitory spectrum and kinetic properties of **protease inhibitor** in **bee venom**. Shkenderov S.. Inst. State Contr. Drugs, Sofia, Bulgaria. Toxicon 13/2 (124) 1975. CODEN: TOXIA6. Language: English.

L33 ANSWER 18 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
75098812 EMBASE Document No.: 1975098812. Anaphylactogenic properties of **bee venom** and its fractions. Shkenderov S.. Inst. State Contr. Drugs, Sofia, Bulgaria. Toxicon 12/5 (529-534) 1974. CODEN: TOXIA6. Language: English.

AB The author investigated the anaphylactogenicity of whole **bee venom** and its pure protein and peptide components (phospholipase A, melittin and apamin) and the partially purified protein and peptide fractions (the highest mol wt fraction I, hyaluronidase, fractions Op, P1 and P2 and **protease inhibitor**) obtained by means of gel filtration and ion exchange chromatography. Anaphylactogenicity was observed with the whole **bee venom** and the high mol wt protein fractions: fraction I, phospholipase A and hyaluronidase. The peptides melittin, apamin, fraction Op (mast cell degranulating peptide, MCD) and fractions P1 and P2 did not show any anaphylactic properties after sensitization with or without Freund's complete adjuvant.

L33 ANSWER 19 OF 19 MEDLINE DUPLICATE 7
73248122 Document Number: 73248122. PubMed ID: 4728973. A **protease inhibitor** in **bee venom**. Identification, partial purification and some properties. Shkenderov S. FEBS LETTERS, (1973 Jul 15) 33 (3) 343-7. Journal code: EUH; 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

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L36 172 DUP REMOVE L35 (242 DUPLICATES REMOVED)

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L37 19 L36 AND BEE

=> dup remove l37

PROCESSING COMPLETED FOR L37
L38 19 DUP REMOVE L37 (0 DUPLICATES REMOVED)

=> d l38 1-19 cbib abs

L38 ANSWER 1 OF 19 MEDLINE
2001226583 Document Number: 21142832. PubMed ID: 11207323.
Antigen-independent suppression of the allergic immune response to **bee** venom phospholipase A(2) by DNA vaccination in CBA/J mice.

Jilek S; Barbey C; **Spertini F**; Corthesy B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166 (5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee** venom allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L38 ANSWER 2 OF 19 MEDLINE
2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new **bee** venom allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee** venom (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry. RESULTS: Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence homology with known proteins. CONCLUSIONS: We have identified and

sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L38 ANSWER 3 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2001:201112 The Genuine Article (R) Number: 405RE. Antigen-independent suppression of the allergic immune response to **bee** venom phospholipase A2 by DNA vaccination in CBA/J mice. Corthesy B (Reprint); Jilek S; Barbey C; **Spertini F**. Hop Orthoped, Lausanne, Switzerland. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (FEB 2001) Vol. 107, No. 2, Supp. [S], pp. S325-S325. MA 1059. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0091-6749
. Pub. country: Switzerland. Language: English.

L38 ANSWER 4 OF 19 MEDLINE
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB To assess the capacity of a peptide-based immunotherapy to induce systemic tolerance via the nasal route, we designed three long overlapping peptides of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee** venom allergen. Both prophylactic and therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

L38 ANSWER 5 OF 19 MEDLINE
2000386468 Document Number: 20354865. PubMed ID: 10898500.
Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner

A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6)
1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee** venom allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44-
to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift
from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L38 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee** venom hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G.
CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO
63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L38 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenecity trial with phospholipase A2-derived
long peptides in **bee** venom hypersensitive patients.
Spertini, Francois (1); Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division
of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical Immunology.,
(Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L38 ANSWER 8 OF 19 MEDLINE
1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and T-cell
responses to high-molecular weight allergens from **bee** venom.
Kettner A; Henry H; Hughes G J; Corradin G; **Spertini F.**
(Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1999
Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: **Bee** venom contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee** venom desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee** venom allergens >/= 50 kDa. METHODS: **Bee** venom proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee** venom fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee** venom-hypersensitive patients, IgE recognition pattern of **bee** venom allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins >/= 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee** venom elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee** venom allergy may require careful characterization of such allergens.

L38 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee** venom phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint); vonGarnier
C; Corradin G P; **Spertini F.** CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318
. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L38 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee** venom phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; **Spertini, F. (1)**. (1) Dep. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51. Meeting Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language:

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NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI

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=> s bee venom

L1 7518 BEE VENOM

=> s l1 and polypeptide

L2 502 L1 AND POLYPEPTIDE

=> s l2 and 8 Kd

L3 0 L2 AND 8 KD

=> s l2 and 8

L4 55 L2 AND 8

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L5 3 L4 AND KD

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PROCESSING COMPLETED FOR L5
L6 2 DUP REMOVE L5 (1 DUPLICATE REMOVED)

=> d l6 1-2 cbib abs

L6 ANSWER 1 OF 2 MEDLINE
88082757 Document Number: 88082757. PubMed ID: 2446869. Photoaffinity labeling of the K+-channel-associated apamin-binding molecule in smooth muscle, liver and heart membranes. Marqueze B; Seagar M J; Couraud F. (Laboratoire de Biochimie, Centre National de la Recherche Scientifique Unite Associee 1179, Marseille-France.) EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Dec 1) 169 (2) 295-8. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB High-affinity binding sites for mono[125I]iodoapamin were detected in membranes (**Kd** = 59 pM, Bmax = 24 fmol/mg protein) and cultured cells (**Kd** = 69 pM, Bmax = 2.**8** fmol/mg protein) from rat heart and in membranes from guinea-pig ileum (**Kd** = 67 pM, Bmax 42 fmol/mg protein) and liver (**Kd** = 15 pM, Bmax = 43 fmol/mg protein). Binding was stimulated by K+ ions (K0.5 = 0.3-0.5 mM). Covalent labeling with arylazide [125I]iodoapamin derivatives showed that smooth muscle, liver and heart binding molecules are associated with a 85-87-kDa **polypeptide**. A second strongly labeled 57-kDa component was identified in liver membranes only.

L6 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
87133589 Document Number: 87133589. PubMed ID: 3028799.
Receptor-mediated

endocytosis of apamin by liver cells. Strong P N; Evans W H. EUROPEAN JOURNAL OF BIOCHEMISTRY, (1987 Mar 2) 163 (2) 267-73. Journal code: EMZ; 0107600. ISSN: 0014-2956. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The binding and uptake of the **bee venom** toxin apamin, by guinea-pig and rat liver were studied. Guinea-pig liver plasma membranes contain inhibitable, high-affinity binding sites for [125I]monoiodoapamin: **Kd** = 12.6 +/- 0.8 pM (SE); Bmax = 4.2 +/- 0.2 fmol/mg protein. No binding sites for [125I]monoiodoapamin on rat liver plasma membranes were detected in agreement with the absence of a physiological response to the toxin by rat hepatocytes. [125I]Monoiodoapamin, injected into the portal vein of guinea-pigs, was recovered in an undegraded form in a liver endosome fraction. The uptake of [125I]monoiodoapamin by rat livers was less than 4% of that taken up by guinea-pig livers and there was little evidence of radiolabelled toxin appearing in isolated rat endocytic vesicles. Inhibitable, high-affinity binding sites for [125I]monoiodoapamin were also identified on isolated guinea-pig liver endosomal membranes; **Kd** = 10.6 +/- 3.3 pM; Bmax = 2.5 +/- 0.6 fmol/mg protein. No inhibitable apamin binding sites were detected on rat endosomal membranes. Plasma membranes and endosomal membranes isolated from guinea-pig liver showed a similar spectrum of **polypeptides** to that previously reported for plasma membranes and endosomal membranes isolated from rat liver. The enzymatic composition of guinea-pig endosomes was also similar to that previously reported for rat endosomes. The results indicate that apamin was internalised by receptor-mediated endocytosis by guinea-pig liver cells in an analogous manner to that already shown for a variety of endogenous ligands.

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=> s spertini f?/au

L7          414 SPERTINI F?/AU

=> s l7 and bee venom

L8           45 L7 AND BEE VENOM

=> dup remove l8

PROCESSING COMPLETED FOR L8
L9           19 DUP REMOVE L8 (26 DUPLICATES REMOVED)

=> d 19 1-19 cbib abs
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L9 ANSWER 1 OF 19 MEDLINE DUPLICATE 1
2001226583 Document Number: 21142832. PubMed ID: 11207323.
Antigen-independent suppression of the allergic immune response to **bee venom** phospholipase A(2) by DNA vaccination in CBA/J mice. Jilek S; Barbey C; **Spertini F**; Corthesy B. (Division of Immunology and Allergy, R & D Laboratory, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2001 Mar 1) 166 (5) 3612-21. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Phospholipase A(2) (PLA(2)) is one of the major honey **bee venom** allergens for humans. To assess the long-term prevention of allergic reactions by DNA vaccination, a PLA(2)-CBA/J mouse model was employed using empty or PLA(2) sequence-carrying DNA plasmids. Early skin application of either DNA construct before (prophylactic approach) or after (therapeutic approach) sensitization with PLA(2)/alum led to reduced

PLA(2)-specific IgE and IgG1 titers at 7 mo, with concomitant rise in IgG2a and IgG3. Splenocytes recovered at 5-6 mo after the last DNA administration exhibited a sustained IFN-gamma and IL-10 secretion and reduced IL-4 production. Recall challenge with PLA(2) boosted IFN-gamma and IL-10 secretion, suggesting the reactivation of quiescent memory Th1 lymphocytes. Mice from the prophylactic groups were fully protected against anaphylaxis, whereas 65% of the animals recovered in the therapeutic groups. Th1-polarized immune responses were also active in mice vaccinated with an empty plasmid 32 wk before sensitization with another Ag (OVA). This is the first demonstration that the Ag-coding sequence in DNA vaccine is not necessary to promote immune modulation in naive and sensitized animals for a prolonged period, and has relevance for the understanding of the innate and induced mechanisms underlying gene immunotherapy in long-term treatment of allergy.

L9 ANSWER 2 OF 19 MEDLINE DUPLICATE 2
2001242064 Document Number: 21242713. PubMed ID: 11344362. Api m 6: a new **bee venom** allergen. Kettner A; Hughes G J; Frutiger S; Astori M; Roggero M; **Spertini F**; Corradin G. (Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 May) 107 (5) 914-20. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. OBJECTIVE: The purpose of this study was the identification and characterization of a low-molecular-weight, IgE-binding, **bee venom** (BV) allergen. METHODS: BV proteins were separated by using size exclusion chromatography and HPLC. IgE antibody binding to purified proteins was analyzed by means of immunoblotting, and T-cell response was analyzed by means of proliferation assay. Amino acid sequence was determined with 2 approaches, namely Edman degradation and carboxy terminal analysis with mass spectrometry. RESULTS: Api m 6, which migrated as an 8-kd band in SDS-PAGE, was frequently (42%) recognized by IgE from BV-hypersensitive patients. In addition, PBMCs from BV-hypersensitive patients, as well as from a normal control subject, proliferated in response to this allergen. Api m 6 exists as 4 isoforms of 7190, 7400, 7598, and 7808 d, respectively. Amino acid sequences obtained from HPLC-purified preparations revealed that the isoforms were constituted of a common central core of 67 residues, only differing in the amino- and carboxy-terminal ends. Api m 6 showed no significant sequence homology with known proteins. CONCLUSIONS: We have identified and sequenced a new BV allergen that elicits a strong IgE and T-cell response in a large number of BV-hypersensitive patients. Api m 6 should be considered in the diagnostic and therapeutic approach of BV immunotherapy on the basis of peptides or recombinant proteins.

L9 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
2001:199768 Document No.: PREV200100199768. Antigen-independent suppression of the allergic immune response to **bee venom** phospholipase A2 by DNA vaccination in CBA/J mice. Corthesy, Blaise (1); Jilek, Samantha (1); Barbey, Catherine (1); **Spertini, Francois (1)** . (1) Hopital Orthopedique, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (February, 2001) Vol. 107, No. 2, pp. S325. print.

Meeting Info.: 57th Annual Meeting of the American Academy of Allergy, Asthma and Immunology New Orleans, Louisiana, USA March 16-21, 2001 ISSN: 0091-6749. Language: English. Summary Language: English.

L9 ANSWER 4 OF 19 MEDLINE DUPLICATE 4
2000483268 Document Number: 20432339. PubMed ID: 10975871. Inducing tolerance by intranasal administration of long peptides in naive and primed CBA/J mice. Astori M; von Garnier C; Kettner A; Dufour N; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF IMMUNOLOGY, (2000 Sep 15) 165 (6) 3497-505. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To assess the capacity of a peptide-based immunotherapy to induce systemic tolerance via the nasal route, we designed three long overlapping peptides of 44-60 aa covering the entire sequence of phospholipase A2 (PLA2), a major **bee venom** allergen. Both prophylactic and therapeutic intranasal administrations of long peptides to PLA2-hypersensitive CBA/J mice induced specific T cell tolerance to the native allergen. In prophylactic conditions, this tolerance was marked by a suppression of subsequent specific IgE response, whereas the therapeutic approach in presensitized mice induced a more than 60% decrease in PLA2-specific IgE. This decline was associated with a shift in the cytokine response toward a Th1 profile, as demonstrated by decreased PLA2-specific IgG1 and enhanced IgG2a levels, and by a decline in the specific IL-4/IFN-gamma ratios. T cell transfer from long peptide-tolerized mice to naive animals abrogated the expected anti-PLA2 IgE and IgG1 Ab response, as well as specific T cell proliferation, but enhanced specific IgG2a response upon sensitization with PLA2. These events were strongly suggestive of a clonal anergy affecting more profoundly Th2 than the Th1 subsets. In conclusion, these results demonstrate that allergen-derived long peptides delivered via the nasal mucosa may offer an alternative to immunotherapy with native allergens without the inherent risk of systemic anaphylactic reactions. Moreover, long peptides, in contrast to immunotherapy strategies based on short peptides, have the advantage of covering all potential T cell epitopes, and may represent novel and safe tools for the therapy of allergic diseases.

L9 ANSWER 5 OF 19 MEDLINE DUPLICATE 5
2000386468 Document Number: 20354865. PubMed ID: 10898500. Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis. von Garnier C; Astori M; Kettner A; Dufour N; Heusser C; Corradin G; **Spertini F.** (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jun) 30 (6) 1638-45. Journal code: EN5; 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB To evaluate a long peptide-based allergy vaccine in a murine model, CBA/J mice were sensitized with low dose alum-adsorbed phospholipase A2 (PLA2), a major **bee venom** allergen. Presensitized mice were treated by daily i.p. injections of a mixture of three long overlapping peptides (44- to 60-mer) spanning the entire PLA2 molecule (100 microg/peptide) for 6 consecutive days. This therapeutic approach induced a sharp drop in PLA2-specific IgE, an increase in specific IgG2a, and a marked T cell hyporesponsiveness. T cell cytokine secretion was characterized by a shift from a Th2 to a Th1 profile. Prophylactic treatment of naive mice with long peptides prior to sensitization with PLA2 induced a comparable modulation of B and T cell responses. Upon i.p. challenge with native PLA2, presensitized mice treated with the long

peptide mixture were fully protected from anaphylaxis. This indicated that allergen-derived long overlapping peptides were safe and able to modulate an established Th2 response or to prevent its development. Furthermore, long peptide-based immunotherapy provided clinical protection against anaphylaxis, thus appearing as a promising approach of the therapy of allergic diseases.

L9 ANSWER 6 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
2000:192482 The Genuine Article (R) Number: 287WR. Allergen peptide immunotherapy: Results of a safety and immunogenicity trial with phospholipase A2 derived long peptides in **bee venom** hypersensitive patients. **Spertini F (Reprint)**; Fellrath J M; Kettner A; Dufour N; Frigerio C; Schneeberger D; Leimgruber A; Corradin G.
CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, EPALINGES, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 2000) Vol. 105, No. 1, Part 2, Supp. [S], pp. 1106-1106. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
2000:140491 Document No.: PREV200000140491. Allergen peptide immunotherapy: Results of a safety and immunogenecity trial with phospholipase A2-derived long peptides in **bee venom** hypersensitive patients. **Spertini, Francois (1)**; Fellrath, Jean-Marc (1); Kettner, Alexander; Dufour, Nathalie (1); Frigerio, Christian (1); Schneeberger, Dominique (1); Leimgruber, Annette (1); Corradin, Giampietro. (1) Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne Switzerland. Journal of Allergy and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S378-S379. Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma and Immunology. ISSN: 0091-6749. Language: English. Summary Language: English.

L9 ANSWER 8 OF 19 MEDLINE DUPLICATE 6
1999221995 Document Number: 99221995. PubMed ID: 10202349. IgE and T-cell responses to high-molecular weight allergens from **bee venom**. Kettner A; Henry H; Hughes G J; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1999 Mar) 29 (3) 394-401. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: **Bee venom** contains multiple allergens with a wide distribution of molecular weight. In contrast with conventional **bee venom** desensitization, peptide or recombinant allergen immunotherapy may have to take into account patients' individual patterns of humoral or cellular response. OBJECTIVE: To study immunoglobulin (Ig)E and T-cell responses to high-molecular weight **bee venom** allergens >/= 50 kDa. METHODS: **Bee venom** proteins were separated by size exclusion chromatography and fractions were characterized by one and two-dimensional gel electrophoresis. IgE antibody binding to **bee venom** fractions was analysed by immunoblotting and T-cell responses by proliferation assay. RESULTS: Among 38 **bee venom** -hypersensitive patients, IgE recognition pattern of **bee**

venom allergens varied greatly. IgE bound mainly to phospholipase A2 and furthermore to several proteins >/= 50 kDa (50, 54, 69, 84 and 94 kDa). N-terminal sequences of these proteins showed no homology with known proteins. In addition, peripheral mononuclear cells from patients as well as from nonatopic donors strongly proliferated in response to those proteins. CONCLUSIONS: Although present in low amounts, high-molecular weight allergens from **bee venom** elicit strong IgE and T-cell responses, and may need to be considered as clinically relevant. Therefore, the development of peptide or recombinant protein-based immunotherapy for **bee venom** allergy may require careful characterization of such allergens.

L9 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1999:142906 The Genuine Article (R) Number: 165FC. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J. Astori M (Reprint); vonGarnier C; Corradin G P; **Spertini F**. CHU VAUDOIS, DEPT IMMUNOL & ALLERGY, LAUSANNE, SWITZERLAND; UNIV LAUSANNE, INST BIOCHEM, CH-1015 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 192-192. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1999:136272 Document No.: PREV199900136272. Intranasal administration of long overlapping peptides from **bee venom** phospholipase A2 induces tolerance in hypersensitive CBA/J mice. Astori, M. (1); Von Garnier, C. (1); Corradin, G. P.; **Spertini, F. (1)**. (1) Dep. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp. S51. Meeting Info.: 55th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3, 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
1998:176527 The Genuine Article (R) Number: YW339. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**.. Astori M (Reprint); Kettner A; Frutiger S; Hughes G J; Corradin G; **Spertini F**. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1998) Vol. 101, No. 1, Part 2, pp. 697-697. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: SWITZERLAND. Language: English.

L9 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1998:154406 Document No.: PREV199800154406. Isolation and characterization of a novel 7.6 Kd allergen from **bee venom**. Astori, M.; Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, G.; **Spertini, F.**. Div. Immunol. Allergy, CHUV, Lausanne Switzerland. Journal of Allergy and Clinical Immunology, (Jan., 1998) Vol. 101, No. 1 PART 2, pp. S169. Meeting Info.: 54th Annual Meeting of the American Academy of Allergy, Asthma and Immunology Washington, DC, USA March 13-18, 1998 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749. Language: English.

L9 ANSWER 13 OF 19 MEDLINE DUPLICATE 7
1998341973 Document Number: 98341973. PubMed ID: 9678833. Delineation of

PLA2 epitopes using short or long overlapping synthetic peptides:
interest
for specific immunotherapy. Kammerer R; Kettner A; Chvatchko Y; Dufour N; Tiercy J M; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) CLINICAL AND EXPERIMENTAL ALLERGY, (1997 Sep) 27 (9) 1016-26. Journal code: CEB; 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Venom immunotherapy is definitely indicated in severe systemic anaphylactic reactions to bee stings, but is not devoided of risks of anaphylaxis. Safer methods of immunotherapy need to be developed. OBJECTIVE: To delineate phospholipase A2 T-cell epitopes using short 15mer vs long 40-60mer overlapping peptides, and to approach the potential interest of a venom immunotherapy based on the use of long peptides (1-60, 51-99, 90-134) mapping the whole phospholipase A2 molecule vs a restricted number of immunodominant epitopes. METHODS: Proliferation of a CD8+ T cell depleted peripheral blood mononuclear cell fraction and short-term T-cell lines from unselected **bee venom** hypersensitive patients in response to phospholipase A2 synthetic peptides. RESULTS: Whereas T-cell proliferation to 15mer overlapping peptides was weak, T-cell response to long overlapping peptides was in contrast vigorous in all patients, mostly directed to C-terminal peptide 90-134. Our results did not support the concept of rare dominant T-cell epitopes, and disclosed T-cell responses to multiple epitopes in several patients. No significant IgE-binding to long overlapping peptides was detected except in one patient against peptide 90-134. CONCLUSION: 15mer peptides might not be sensitive enough to fully delineate all potential T-cell epitopes scattered along the allergen. Since they do not bind IgE in vitro or only weakly, and taking into account a T-cell response frequently directed to multiple epitopes, long overlapping peptides may represent ideal tools for immunotherapy.

L9 ANSWER 14 OF 19 MEDLINE DUPLICATE 8

97400299 Document Number: 97400299. PubMed ID: 9257793. Modulation of T-cell response to phospholipase A2 and phospholipase A2-derived peptides by conventional **bee venom** immunotherapy. Kammerer R; Chvatchko Y; Kettner A; Dufour N; Corradin G; **Spertini F**. (Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Jul) 100 (1) 96-103. Journal code: H53; 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Immunologic mechanisms of desensitization are still incompletely understood. Safer methods of immunotherapy with reduced risks of anaphylaxis need to be developed. OBJECTIVE: To study the effects of conventional venom immunotherapy (VIT) on phospholipase A2(PLA2)-specific T cells and on T-cell reactivity to short and long synthetic peptides that map the PLA2 molecule. METHOD: Proliferation of a CD4+ cell-enriched peripheral blood mononuclear cell fraction and cytokine secretion by T cell lines from patients hypersensitive to **bee venom** and undergoing VIT in response to PLA2 and PLA2 synthetic peptides were measured. RESULTS: T-cell proliferation in response to three synthetic peptides, 40 to 60 amino acids long and mapping the entire PLA2 molecule with an overlap of 10 residues (1 to 59, 51 to 99, and 90 to 134) steadily increased during the first 14 weeks of VIT corresponding to the treatment

period with incremental doses of antigen. These results are in contrast to the low proliferation indices obtained with short (15 amino acid-long) peptides, and the inability to characterize the immunodominant region of the molecule with short peptides. At the end of VIT (after 3 to 5 years), there was correspondingly, a marked decrease in T cell responsiveness to PLA2 and to its long synthetic peptides. This response was paralleled by a shift in the pattern of cytokine secretion by T cell lines from a T(H0)-type to a T(H1)-type pattern. CONCLUSION: After a transient increase in T-cell proliferation, late VIT was characterized by T-cell hyporesponsiveness to allergen and by modulation of cytokine secretion from a T(H0)-type to a T(H1)-type pattern. Because of their capacity to recruit multiple T-cell epitopes, long peptides mapping the entire PLA2 molecule appear to be efficient T cell stimulators and may represent potential candidates for peptide immunotherapy.

L9 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
96:400023 The Genuine Article (R) Number: UK861. A NOVEL 7.6 KD ALLERGEN FROM **BEE VENOM** - ISOLATION AND CHARACTERIZATION. ASTORI M (Reprint); KETTNER A; FRUTIGER S; HUGHES G J; CORRADIN G; **SPERTINI F**. CHU VAUDOIS, DIV IMMUNOL & ALLERGY, CH-1011 LAUSANNE, SWITZERLAND; INST BIOCHEM, CH-1066 EPALINGES, SWITZERLAND; CTR MED UNIV GENEVA, DEPT MED BIOL, CH-1211 GENEVA, SWITZERLAND. FASEB JOURNAL (30 APR 1996) Vol. 10, No. 6, pp. 2764. ISSN: 0892-6638. Pub. country: SWITZERLAND. Language: ENGLISH.

L9 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310225 Document No.: PREV199699032581. T cell epitope mapping with short or long synthetic peptides. Kettner, A. (1); Chvatachko, Y.; Kammerer, R.; Dufour, N.; Corradin, G. (1); **Spertini, F.**. (1) Inst. Biochem., 1066 Epalinges Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 17 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1996:310226 Document No.: PREV199699032582. A novel 7.6kD allergen from **bee venom**: Isolation and characterization. Astori, M. (1); Kettner, A.; Frutiger, S.; Hughes, G. J.; Corradin, C.; **Spertini, F. (1)**. (1) Div. Immunol. Allergy, Cent. Hosp. Univ. Vaudois, 1011 Lausanne Switzerland. FASEB Journal, (1996) Vol. 10, No. 6, pp. A1479. Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June 2-6, 1996 ISSN: 0892-6638. Language: English.

L9 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:383183 Document No.: PREV199598397483. T cell response to **bee venom** allergens: Modulation by specific immunotherapy. Kammerer, R. B. (1); Chvatchko, Y. (1); Kettner, A. J.; Corradin, G.; **Spertini, F.**. (1) Div. Immunol. Allergy, CHUV, Lausanne Switzerland. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 436. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the

International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

L9 ANSWER 19 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
1995:381846 Document No.: PREV199598396146. T-cell and IgE response to partially purified **bee venom** (BV) allergens. Kettner, A. J. (1); Chvatchko, Y.; Kammerer, R. B.; Corradin, G.; **Spertini, F.**. (1) Inst. Biochem., Lausanne Switzerland. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 208. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995 Language: English.

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L1          7518 S BEE VENOM
L2           502 S L1 AND POLYPEPTIDE
L3             0 S L2 AND 8 KD
L4            55 S L2 AND 8
L5             3 S L4 AND KD
L6             2 DUP REMOVE L5 (1 DUPLICATE REMOVED)
L7           414 S SPERTINI F?/AU
L8            45 S L7 AND BEE VENOM
L9            19 DUP REMOVE L8 (26 DUPLICATES REMOVED)
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=> s l4 and IgE binding

4 FILES SEARCHED...

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L10            4 L4 AND IGE BINDING
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L11            1 DUP REMOVE L10 (3 DUPLICATES REMOVED)
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L11 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
92113252 Document Number: 92113252. PubMed ID: 1730869.
Glycosylation-inhibiting factor from human T cell hybridomas constructed from peripheral blood lymphocytes of a **bee venom** -sensitive allergic patient. Thomas P; Gomi H; Takeuchi T; Carini C; Tagaya Y; Ishizaka K. (La Jolla Institute for Allergy and Immunology, CA 92037.) JOURNAL OF IMMUNOLOGY, (1992 Feb 1) 148 (3) 729-37. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Human T cell hybridomas, which constitutively secrete glycosylation inhibiting factor (GIF), were constructed from PBL of an allergic individual who was sensitive to honey **bee venom**. PBMC of the patient were stimulated with either denatured or cyanogen bromide-treated **bee venom** phospholipase A2 (PLA2), and Ag-activated cells were propagated by IL-2 in the presence of human recombinant lipocortin I. T cells obtained in the cultures were fused with

a HAT-sensitive mutant of the human lymphoblastoid cell line CEM. Approximately one-third of hybridoma clones constitutively secreted GIF. The GIF-producing hybridomas were CD3+ and bore TCR-alpha beta. GIF formed by unstimulated hybridomas lacked affinity for **bee venom** PLA2. Upon cross-linking of CD3, however, a majority of the GIF-producing hybridomas formed **IgE-binding** factors and GIF, the latter of which had affinity for **bee venom** PLA2. Both nonspecific GIF and Ag-binding GIF from the hybridomas bound to an immunosorbent coupled with the anti-lipomodulin mAb 141-B9. Using an affinity-purified GIF as an immunogen, we established mouse B cell hybridomas that secreted monoclonal anti-human GIF. In order to characterize human nonspecific GIF, one of the GIF-producing hybridomas was adapted to a serum-free medium, and culture supernatant was fractionated by DEAE-Sepharose column chromatography and by gel filtration. The majority of nonspecific GIF in the culture supernatant was recovered from DEAE-Sepharose by elution of the column with 10 mM Tris-HCl buffer, pH **8**.0, containing 50 mM NaCl. Affinity-purification of GIF in the DEAE Sepharose fraction by using anti-GIF-coupled Affigel, and analysis of the purified GIF by SDS-PAGE revealed that human GIF is a single **polypeptide** chain of 14 to 15 kDa. Gel filtration of both crude and affinity-purified GIF preparations confirmed the molecular size of the cytokine.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	52.79	52.94

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STN INTERNATIONAL SESSION SUSPENDED AT 14:22:54 ON 16 JUL 2001